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LETTER FROM THE EDITORS

Morgan Sheridan and Lauren O’Rourke
Medical Student Journal of Australia, Volume 5, Issue 2

Welcome!

It is sometimes tempting to think “Does a student journal really matter?” Admittedly biased, we believe that even with all the other outlets for publication, a student journal is uniquely placed to highlight the ideas and efforts of the future generation of health care professionals. The MSJA gives students and junior professionals a place to publish their thoughts and theories. It is a place of expression for young professionals that hopefully encourages them to not only continue their engagement with research, but also nurture their creativity.

Previously in the MSJA, we announced that submissions were now accepted from allied health and junior health professionals as well as from medical students. We have also worked to expand our readership which has resulted in submissions from students and junior professionals in Malaysia and New Zealand. This broader authorship will appeal to a wider audience, and also offer a larger number of submissions in which to find quality content for the journal.

An important question for the MSJA has always been how to best spend our limited resources to best reach our readers. Given our expanding readership and the continual advances in modern technology, we have decided to transition the MSJA to a purely online publication. This change will allow us to better engage our large and sometimes far-flung readership, but also ensure the image quality required to best represent our photographs, figures, and artworks without breaking our budget. This change will also allow us to divert our print budget into re-designing our website.

The new MSJA website, to be launched later this year, will have its own domain name (msja.edu.au) and have a responsive design for better display on mobile devices and tablets. The new website will be easier to update, and allow MSJA staff to make each issue available more quickly. All content in the new website will have searchable tags to make it easier for readers to search for articles. It also takes steps towards meeting another long term goal of the MSJA, to have our content indexed on scholarly databases such as PubMed and Google Scholar.

Without the cost of printing, the MSJA will also be able to divert resources into other areas to help develop other components of the journal. We have exciting plans in the development stages and encourage you to keep an eye out for future editions to find out more.

All in all, we hope all these changes continue to mean better and more accessible content for our readers!

Morgan Sheridan and Lauren O’Rourke
Editors-in-chief
When Megan Hickie asked me to write an autobiographical note for Medical Students Journal of Australia, I feared that I might fall into the trap of self-indulgence, telling you how to live your lives and make career decisions. But US political satirist Russell Baker set me straight. He said at the start of a graduation address, “The graduation speaker tells the graduates to go forth into the world then gives advice on what to do when they get out there. This is a ridiculous waste of time. Graduates never take advice, as I have learned from long experience. But (if you want it) the best advice I can give anybody about going out into the world is this: Don’t do it. I have been out there. It is a mess.” So, no advice from me – just observations and reflections.

When I look at my own career and at the careers of the people who graduated with me, two things stand out. The first is that those who had clear goals often achieved them. Goals are big. Goals have to do with your sense of purpose. They matter. They energise. They create opportunities.

But the second is that plans don’t matter anywhere near as much as goals. Yes, plans are important matters of detail, usually about what we are aiming to do now and in the near future. Plans are means to ends. Plans are maps. But plans are usually made of paper and fall apart in the rain. In my life when plans came apart, often something better was the cause. I have seen this happen with many colleagues. When one lot of plans disintegrated, they reached their goal by a new, more interesting, imaginative route.

Let me give you a couple of examples from my own life.

Forty-six years ago in 1967 I was completing my second year as an intern at Royal North Shore Hospital in Sydney. My goal was to train as a physician. Then – boom! – a friend in Papua New Guinea who worked on a mission station in the highlands wrote to me and asked if I would consider filling in for a year – 1968 – between permanent doctors at a hospital in Baiyer River in the western highlands.

Why not? I thought. Colleagues said to me, “You’re crazy! Stick with your original plan! North Shore won’t have you back when you’ve finished your adventure! You’re stuffing your career!” Well, I spent 1968 in Papua New Guinea and in 1969 North Shore did take me back as a registrar and I trained as a physician.

That serendipitous change of plans in 1968, that year of only apparent detour, showed me what amazing things you can do with preventive medicine. My predecessors in Papua New Guinea had immunised the Enga children. When a whooping cough epidemic struck our valley in September, our children were safe. None of the children among the 14,000 people we cared for directly got sick. But our hospital was inundated with children with whooping cough from other highland villages, and from outside our catchment area, several of whom died.

Also, because of the circumstances of that year I developed a lifelong interest in population research. There was a lot of chronic respiratory disease in the highlands not due to tobacco smoke but possibly due to early infections and smoke pollution of the huts. At a medical conference that year Richard Lovell, then professor of medicine at Melbourne, took an interest in me and said, “Why don’t you do epidemiology?” I wasn’t sure what that was, but it sounded good. Back in Sydney this led to my PhD project. I trained as an epidemiologist. Please note that none of this was on my 1967 plan – none of it! In a few short years the plan for reaching my overall career goal had taken a direction I had never anticipated, even though the overall goal itself of wanting to be a useful physician remained steadfast.

Let me give you another very brief example. In 1975, as a post-doctoral student working in London and then in Canada, I was one day contacted from nowhere by the founding dean of a new medical school in Newcastle New South Wales to ask if I would do two things – contribute to a brand new medical curriculum based on problem solving that engaged students with the community and initiate programs in community based research.

I had absolutely no knowledge of this option when I began my post-doc but I did have a longstanding interest in medical education and this combination was irresistible. A long standing goal to contribute to the development of medical education led to a plan to go to Canada. But in a year I was back in Australia pursuing it with an entirely different plan.

The landscape of the rest of my career is equally littered with damp plans that have fallen apart. In 2003 my family and I were planning to leave for Boston where I was going to work at Harvard with Jeffrey Sachs, a leading macroeconomist, on the economics of health in developing countries. Three months before we were due to leave he wrote apologising that he had just moved to Columbia University in New York and perhaps therefore we might not wish to join him. Imagine anyone apologising for moving to New York!

Anyway, it took me all of several microseconds to compose a response. ‘Jeff,’ I said, ‘Don’t worry! We’ll come to New York, too!’ We did and it proved to be a truly wonderful eighteen months. The work on heart disease in the developing world was done but quite differently, and with different but co-workers, and new friends, in ways that I had not anticipated. On the personal side, in New York with its pressure to perform and reach your potential, I was stimulated to rekindle my interest in writing poetry.

Now my point is this. An overarching goal is essential for if you don’t know where you’re going any road will take you there. But don’t put on blinkers and get too locked into following just one of the many road plans or road maps that will take you to your overarching goal. Certainly you do need a plan, just as you need a grocery list when you go food shopping. But be open to the possibility that when you get to the supermarket some items may be on sales that are more attractive and useful than what you had on your list.
Look at the lives of achievers and contributors to society, take time to read their biographies and autobiographies, make careful note of how they have coped when chance disrupted their plans.

American theologian William F. May speaks of “openness to the unbidden”. By that he meant a quality of open-mindedness about the things that occur in our lives by chance. Such openness – almost a whimsical welcome and anticipation, to the unbidden – has led to outstanding scientific discoveries. It also keeps us humble and stops us from falsely imagining that we are masters of the universe. The roll of the dice of chance can of course sometimes be unnerving and distressing and not everything that happened by chance to my colleagues or to me has helped us achieve our grand goals.

In the vast majority of cases when your career road plan or road map presents you with an unexpected turn, do not reject it. Welcome it and check it out. Often chance is throwing the ball to you and inviting you to imagine something different, a new game, about how, under changed circumstances, you may press towards your goal. It can give you new freedom and fresh energy.
A topic autoimmune diseases have a massive impact on society (1) with the incidence and severity of these disorders steadily increasing in developed countries (2). This trend has also been seen in developing countries, especially in urban areas (3). One rationalisation for this trend is to evoke the hygiene hypothesis, which states that syndromes associated with allergy/inflammation occur more frequently in regions subject to stringent hygiene practices, because of a lowered pathogen burden (2). Whilst other factors such as increased pollution and widespread use of antibiotics contribute to this trend (4), data is accruing that implicates helminthic infections as a protective agent against Th-2 driven atopic/autoimmune/inflammatory disease (3). This begs the obvious question: Could there be a role for helminth-based therapies in the treatment of atopic/allergic conditions?

Certainly, it has been well documented that children infected with intestinal helminths, especially hookworm species, have a reduced incidence of allergic responses (5). This protective effect is ameliorated by anti-helminthic therapy: with atopic responses to allergens being stronger after eradication of helminths (6). Animal models also suggest a protective role for helminths. For example, mice infected with the hookworm Heligmosomoides polygyrus show reduced allergic responses (7). However, this protective effect does not appear true to all helminths. Studies have shown that certain helminth infections may exacerbate allergic responses in both animal and human models (8-10). Thus, it appears that whilst some helminths favour the generation and exacerbation of an allergic immune response, others afford protection. Harnessing this protective mechanism offers a novel mechanism for the protection against these conditions.

The immunological substrate behind the putative protective effects of helminths has been extensively studied (3). In brief, they relate to the ability of helminths to induce a polyclonal Th2 IgE derived response and the development of regulatory T cells and alternatively activated macrophages. The polyclonal IgE response saturates binding sites on mast cells, eosinophils and basophils whilst Treg and APCs cells directly or indirectly inhibit allergen-driven Th2 proliferation, a central mechanism towards the development of allergy/atopy (3).

To date, the number of trials evaluating the benefits of helminth-based therapies has been sparse. Trichuris suis has been studied and shown to be efficacious in the treatment of active Crohn’s disease (11). In vitro evidence has shown that extracts of H. diminuta alleviate chemically induced colitis in mice with greater potency than daily corticosteroid therapy (12).

Whilst these results are exciting, further research must progress with caution. Indeed, gastrointestinal helminths have the potential to cause harm to the host, limiting their use. Aside from fulminant infection, there is the potential for immune suppression by the chronic anti-inflammatory response that occurs with infection (3). The side effects of helminth therapy have yet to be properly studied (3). Regardless, helminth-based therapy offers a novel means of treatment for allergic/atopic/autoimmune conditions. Future research into this field is required before any clinical recommendations can be made regarding the safe and effective-use of helminths in the treatment of these medical significant conditions.

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3. Erb KJ. Can helminths or helminth-derived products be used in humans to prevent or treat allergic diseases? Trends Immunol. 2009 Feb;30(2):75-82.
What if you could look at a page, section, even chapter in a text book once and then recall it perfectly from memory? What if clear, logical, concise arguments and clinical reasoning were at your fingertips? Would you take a pill that could make you… limitless?

While there is currently no drug like NZT-48 from the film Limitless (2011, Rouge Pictures) on the market today, there are a number of drugs available which improve memory, alertness, concentration and reduce the risks of impulsive behaviour and dangerous decision making (1-3). The majority of these are regularly prescribed by doctors for conditions such as attention deficit hyperactivity disorder (ADHD), fatigue and narcolepsy. The most commonly used drugs are methylphenidate (Ritalin), Adderall (mixed amphetamine salts) and modafinil (Provigil). Demand for these and other novel drugs looks only to increase for medical reasons in the presence of an aging population suffering from declining cognitive function and diseases such as Alzheimer’s. While the younger demographic faces increasing pressure to perform academically in exams, research, publication and extracurricular activities just to remain competitive. This could push students to the use of these cognitive enhancers to give them an edge.

There has been considerable ethical debate in the literature on the use of these drugs, in particular methylphenidate, as cognitive enhancement or neuroenhancement in otherwise healthy individuals (4, 5). Emerging data from the United States (US) suggests around 7% to as many as 35% of college students at some institutions are taking non-medical prescription stimulants to improve grades, concentration and alertness (6). An impromptu survey of its readers by the journal Nature in 2008 revealed 1 in 5 respondents had used neuroenhancement for non-medical reasons; the most popular reasons being improving focus and concentration, through to assessing the validity of articles on the topic (7). Data from Australia is virtually non-existent, however data from 2002 – 2009 showed a 87% increase in stimulant dispensing overall and a 300% increase in prescriptions of methylphenidate (8). Should we be concerned about these trends, and what implications does cognitive enhancement through pharmaceutical use have on education and medical practise? This article will look at some of the current opinions surrounding this issue namely (1) what constitutes cognitive enhancement; (2) is cognitive enhancement cheating; (3) indirect coercion in the workplace and educational institutions; (4) perceptions in the media, academia and public health institutions; (5) potential for harm and addiction.

The pursuit of knowledge and the desire to enhance ones cognitive abilities are as old as time. Human ingenuity has developed written language, education and technology. These arguably raise our effective cognitive abilities beyond that of our normal biological brains. Mental tricks and frameworks of thinking are imparted to us throughout our lives to improve our performances in certain areas and are considered a conventional form of cognitive enhancement (9). Doctors promote healthy eating and exercise to improve mental acuity and improve overall health. We use caffeine, ginkobiloba and high calorie energy drinks as legitimate attempts to enhance alertness, concentration and memory. Many authors would argue pharmacological cognitive enhancement, while unconventional, should be considered as a part of the same category; some authors believe that many users already perceive it as such (4, 10, 11). But should these drugs be considered a valid mode of cognitive enhancement, or is their use tantamount to cheating?

A common argument against the use of cognitive enhancement drugs is that they constitute cheating or gaining an unfair advantage, with the common analogy drawn to sport and its anti-doping rules (11, 12). There is an important distinction between the two: in sport, doping is breaking an explicit rule set out by a governing body. In education, the rules are rarely explicit. The Australian National University exam policies are not prescriptive on how...
students prepare for an exam. It is perhaps assumed a student will diligently revise the course material over an adequate period. But what if a cognitive enhancer could halve or even quarter the time required to learn the content for an exam. If they were only available to select students this would constitute an unfair advantage. However, the same could be said for private tuition, computer access at home and childhood nutrition (11). If, like electronic calculators, these methods were available to everyone, then there is no reason to limit their use. Of course rules should be modified based on the intent of the exam; assessing memory, a particular skill or selecting candidates. However, when used in the appropriate contexts, cognitive enhancement could be used to promote educational excellence.

If the pervasiveness of cognitive enhancement increases, will there be greater pressure on students and perhaps even qualified doctors to conform to stay competitive with their peers? This statement requires several assumptions; first, that the cognitive enhancement provides a vast improvement in academic and workplace performance; second, that the top students and doctors require enhancement to stay at the top; and third, that it is prohibitively difficult to achieve the same level of performance independent of enhancement (11). However, restricting people’s actions based on how it will affect others is not a legitimate reason for prohibition. For example, a financially independent student would not be expected to limit the amount of time they dedicate to study to achieve equality with a student who has to work several jobs to support themselves. In the workplace it could be argued that there are already pressures to conform to obtain qualifications and publish papers. Nevertheless, as one author astutely points out, just because these pressures already exist does not justify their expansion into other areas (5). Internal pressures are not the only consideration; public perception is just as important. What if in the future patients demanded access to cognitively enhanced surgeons and physicians?

A recent article by Forlini C. and Racine E. explored the differing portrayals of print media, bioethics literature and public health literature on the use of methylphenidate (13). Different sources reported different aspects of the issue, with print media highlighting the lifestyle choice of cognitive enhancement as a laudable act, bioethics literature looking at the presumed benefits of the use of neuroenhancers by healthy individuals and public health literature using the terms ‘abuse’ and ‘illicit use’ to highlight a public health problem. This highlights the divided opinions on the topic and may promote an unintended propagation of non-medical prescription use (6). With limited empirical data on the effects these drugs have in healthy people, there needs to be further research into the potential harms and long-term side effects before any promotion in the media is endorsed by public health authorities.

The majority of health interventions, with the obvious exception of cosmetic enhancement, seek to treat or manage a deficit in an individual’s health. Drug approvals for these conditions take this into account when assessing risk against benefits. Cognitive enhancement in the healthy is a far greyer area. What is an acceptable risk or side effect profile when you are managing a healthy individual? Intuitively, it could be argued that it needs to be extremely low. However alcohol and smoking are two examples of widely used drugs in the community which cause both disease and addiction. That is not to advocate in favour of dangerous cognitive enhancement, but it does highlight the level of risk otherwise healthy individuals are willing to expose themselves to for social gain. As a profession the medical community, who are currently the gatekeepers of these substances, should consider how to appropriately distribute them. Any substance which directly affects the brain has some potential for addiction, but current drugs such as modafinil show an alarming level of addiction potential by promoting dopamine release in the ventral striatum (5). But should the nature of current drugs in use as cognitive enhancement necessarily preclude research into novel neuroenhancers?

In conclusion, our growing ability to alter brain functions and enhance mental processes is leading to a foreseeable age of pharmaceutical cognitive enhancement. Guidelines and regulations need to be pre-emptively enacted to ensure cognitive enhancement is used appropriately in the community. Professional bodies must show leadership, and ensure that distribution of these substances is controlled and regulated. Furthermore, the public needs to be informed of the risk, benefits and alternatives to these emerging trends.

Conflicts of interest: nil
Acknowledgements: nil

References:
Depression as a risk factor for cardiovascular disease—systematic review and meta-analysis

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Declaration of Conflict of Interest: None declared.

Abstract

Objective: The aims of this study were to update and extend the evidence and to estimate the extent to which depression in adult life is a risk factor for the development of cardiovascular disease.

Methods: A meta-analysis of longitudinal cohort and case-control studies reporting depression at baseline and cardiovascular outcomes (including stroke) at follow-up was conducted. Studies using both self-reported information and medical records were included. Other inclusion criteria were: participants free of cardiovascular disease at baseline (or controlled for in analysis), community-dwelling or general practice samples; and exposure of at least 12 months. The search was done in PubMed.

Results: Participants with depression were estimated to be 38% more likely to develop non-fatal cardiovascular disease (pooled estimate 1.38, 95% confidence interval: 1.16, 1.64), and 35% more likely to experience a fatal cardiovascular event (pooled estimate 1.35, 95% confidence interval: 1.17, 1.56) over an average 13 years of follow-up.

Conclusions: This study has contributed to the body of research identifying depression as a risk factor for developing cardiovascular disease, which has important implications for clinicians managing patients with depressive illnesses.

Key words: cardiovascular diseases, depression, review.

Introduction

There is a growing body of literature demonstrating a link between cardiovascular disease and depression. This relationship is bidirectional (1); not only do people with cardiovascular disease experience higher rates of depression (2), but several studies indicate that depression itself is a risk factor for cardiovascular disease (3-7). Van der Kooy et al. (8) undertook a systematic review and meta-analysis of the literature to January 2005 and found that depression was an independent risk factor for cardiovascular disease.

Cardiovascular disease is the leading cause of death in Australia, the United States of America (USA), and overall worldwide (9). On average, more than 2,200 people in the USA die from cardiovascular disease every day, with coronary heart disease and stroke being responsible for one in six and one in 18 deaths in 2007, respectively (10-12). Over one-third of American adults are estimated to have one or more forms of cardiovascular disease, which includes hypertension, coronary heart disease, heart failure and stroke (10). Cardiovascular disease is also an important health priority in Australia with ischaemic heart disease and cerebrovascular disease accounting for 16% and 8% of all deaths in 2009, respectively (9). In 2004-05, around 3.5 million Australians—about 18% of the population—reported having a long-term cardiovascular condition (13), and 14% of them reported having a co-existing mental/behavioural health problem (13). Cardiovascular disease accounted for 18% of the total burden of disease (measured in disability-adjusted life years) in Australia in 2003 (14). Ischaemic heart disease attributable to anxiety and depression was estimated to account for 0.3% of the total burden of disease, which is comparable to the burden of disease due to osteoporosis.

Objectives: The primary purpose of this paper is to update the evidence for depression as an independent risk factor for all cardiovascular diseases.

Secondary objectives: Secondary objectives for the paper are to investigate the evidence for depression as a risk factor for sub-types of cardiovascular diseases. Study outcomes included fatal or non-fatal cardiovascular disease of any kind, coronary heart disease, acute myocardial infarction, stroke and angina. Studies including participants with pre-existing cardiovascular disease matching the outcome or that did not control for this in statistical analyses were excluded.
Methods

Identification and selection of literature: A systematic literature search was conducted using the PubMed database, including articles published up to and including 24 October 2010 (the census date). The following search terms were used (where an asterisk represents word truncation), searching in titles and abstracts: cardiovascular disease*, myocar-dial ischemia, myocardial ischaemia, coronary, infarct*, ischemic, heart attack, angina; and depress*, mood disorder, dysthymia. Papers were limited to those with abstracts, studies on humans, and journal articles in English.

The citations resulting from the PubMed search were downloaded into EndNote and screened by KO based on title. Abstracts were then double-screened by two reviewers (KO and one of KA or NC). Those papers included after the first screening stage were printed and assessed by two reviewers (as above) for suitability against the selection criteria. Where decisions on inclusion were inconsistent, these were discussed by the authors for final assessment.

Selection criteria were as follows:
Study type: longitudinal case-control or cohort studies
Eligible populations: community-dwelling or general practice samples; participants free of cardiovascular disease at baseline or excluded in the analysis; minimum sample size of 100
Exposure: depressive symptoms / disorders assessed at baseline; minimum exposure of 12 months
Outcome measures: any cardiovascular disease (fatal or non-fatal)

Exposure variables were included if they were based on a measure of depression for which validation data has been published in the peer-reviewed literature, were measured by a standard self-report questionnaire, or if they were validated self-reported data.

Outcome data were stratified into: a) self-reported cardiovascular morbidity; b) morbidity determined from medical records; and c) mortality determined from death certificates and/or medical records.

Data extraction:
Selected articles had the following data extracted from them, where available: study name, location and design; number of study participants, mean age and proportion female; observation period; depression measure and validation; outcome measure; factors adjusted for; source of outcome data; adjusted risk estimates (hazard ratios, risk ratios, odds ratios) (or crude risk estimates if no adjusted estimates were published).

Exposure data was classified as dichotomous, categorical, or continuous. Where the exposure was categorised into more than two groups, the most extreme comparison was used against the baseline.

Outcomes were broadly classified as: all cardiovascular diseases (equivalent to ICD-10 chapter I); cardiovascular disease excluding stroke (ICD-10 chapter I excluding sections I60-I69); cerebrovascular disease (ICD-10 sections I60-I69).

A number of studies presented data for more than one outcome (e.g. fatal and non-fatal cardiovascular disease separately; all cardiovascular disease and selected subsets such as myocardial infarction or stroke). In these cases, for analyses with all cardiovascular disease as the outcome, the reported data including the most comprehensive data was used. For example, if a study reported on all cardiovascular disease and coronary heart disease alone, the all cardiovascular disease result was included in the analysis for all cardiovascular disease as outcome, and the coronary heart disease result was included in the analysis for CHD/AMI only.

If a study reported on say coronary heart disease and stroke separately (but not combined), these were both included in the all cardiovascular disease analysis.

Where multiple publications from the same study were identified through the selection process, the study with the largest number of subjects was included. Where two studies used the same data source but reported on different outcomes (e.g. coronary heart disease in one, stroke in another), both studies were included.

Analysis:
For the purposes of the study, all adjusted risk estimates—risk ratios (RR), odds ratios (OR) and hazard ratios (HR)—were considered equivalent. When an outcome is of low incidence, this is generally considered an acceptable assumption, and is consistent with previous studies (8, 15). Where more than one risk estimate was published for an outcome, the most adjusted estimate was extracted.

Meta-analysis was undertaken using Review Manager 5.1. Analysis was undertaken for outcomes of mortality only, non-fatal and/or fatal disease, and non-fatal disease only. Sub-group analysis was done for men and women where possible.

Where four or more studies were included in the analysis, heterogeneity was assessed using the I2 statistic, which measures the proportion of variability in effect estimates due to heterogeneity rather than sampling error (16). The Cochrane Handbook (16) suggests that values for I2: <40% may not be important; 30-60% may represent moderate heterogeneity; 50-90% may represent substantial heterogeneity; 75-100% considerable heterogeneity. In this study, where I2 was greater than 50%, heterogeneity was considered present and statistical pooling was done using random effects analysis. Where I2 was less than 50% or there were three or fewer studies, fixed effects analysis was used. This is consistent with the approach taken by Anstey et al. (15). Sensitivity analysis was also undertaken to determine whether lower quality studies were significantly contributing to heterogeneity of results. Twenty-three studies classified depression as dichotomous or categorical, six as continuous, and one used both approaches. Heterogeneity was minimised by separating analysis for dichotomous/categorical and continuous exposure data.

Results

Selection of studies:
The literature search identified 10,339 articles. The majority of these included terms on ST-segment depression, a component of an electrocardiogram (ECG) which is a tool used to analyse electrical activity of the heart. This led to many irrelevant papers being excluded after the initial search.

The flowchart (Figure 1) shows the steps that reduced the 10,339 papers to the 30 papers included in the analysis (3-6, 17-42).

Study characteristics:
Characteristics of included studies are given in Tables 1 and 2.

The 24 included studies with dichotomous/categorical exposure comprised...
nearly 287,000 subjects. The mean number of participants was approximately 13,000, and the mean follow-up time was 13 years (range 3.2–37 years).

Eleven of these studies found a significant positive relationship between depression and incident cardiovascular disease (non-fatal and/or fatal).

Quality assessment:
The following quality assessment criteria were assessed: all pre-existing cardiovascular diseases excluded from the study or final analysis; depression measured through a validated questionnaire; control for antidepressant medication; follow-up of 10 years or more (median of studies); sample size of 1,000 or more; medical records not used as sole/primary source of outcome; basic demographic information (age, sex) given for final study population; adjusted risk estimates published. Scoring was positive (+), negative (-) or indeterminate (?). Results of the quality assessment are shown in Table 3.

These assessment criteria were developed through analysis of similar systematic reviews, e.g. Van der Kooy et al. (8).

The studies with the highest score were Bremmer et al. (3) and Whang et al. (40) with seven out of a possible eight points. Two studies scored only three points (17, 19). Overall, 21 studies scored five or more points, and nine less than five points.

Meta-analysis

Fatal cardiovascular disease only:
Twelve studies were included with published results for cardiovascular disease mortality, representing nearly 190,000 participants; approximately 17,250 on average (range 192 to 73,098). The mean follow-

![Figure 1. Article identification for inclusion in the meta-analysis.](image)

<table>
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<th>Study name (source)</th>
<th>Observation period, years (SD)</th>
<th>Depression measure</th>
<th>Outcome measure</th>
<th>Mean age, years (SD)</th>
<th>Proportion female (%)</th>
<th>Risk type</th>
<th>Factors adjusted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahto, 2007 (661)</td>
<td>Lieto Health Centre, Finland</td>
<td>12</td>
<td>Zung Self-rating Depression Scale ≥ 45</td>
<td>Mortality due to CHD/MI (ICD-10 codes I20-I25)</td>
<td>M: non-depressive 71.1 (6.3), depressive 71.5 (6.2); W: non-depressive 71.3 (5.8), depressive 72.9 (5.8)</td>
<td>57</td>
<td>HR</td>
<td>none</td>
</tr>
<tr>
<td>Bremmer, 2006 (2,403)</td>
<td>Longitudinal Aging Study Amsterdam (LASA), The Netherlands</td>
<td>7.2</td>
<td>CES-D ≥ 16</td>
<td>First cardiac event (fatal or non-fatal)</td>
<td>69.4</td>
<td>54.3</td>
<td>RR</td>
<td>age, sex, education, marital status, excessive drinking, smoking, BMI, abdominal obesity, hypertension, diabetes, cognitive impairment, use of selective serotonin reuptake inhibitors or tricyclic antidepressants</td>
</tr>
<tr>
<td>Study (Year)</td>
<td>Location</td>
<td>Sample Size</td>
<td>Methodology</td>
<td>Intervention</td>
<td>Outcomes</td>
<td>Follow-up</td>
<td>Analysis</td>
<td>OR/RR</td>
</tr>
<tr>
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</tr>
<tr>
<td>Emparna, 2006 (2,751)</td>
<td>Group Health Cooperative of Puget Sound, western Washington State, USA</td>
<td>Not given</td>
<td>Physician diagnosed clinical depression</td>
<td>Out of hospital cardiac arrest</td>
<td>Cases: 63.1 (11.9); Controls: 63.8 (11.1)</td>
<td>Stroke mortality (ICD-9 400-436)</td>
<td>43.4 (15.9) (whole sample)</td>
<td>54.2 (whole sample)</td>
</tr>
<tr>
<td>Everson, 1998 (6,417)</td>
<td>Alameda County Study, USA</td>
<td>29</td>
<td>Human Population Laboratory Depression Scale ≥ 5</td>
<td>CHD (fatal and non-fatal) (ICD-9 410-414)</td>
<td>M: 55.9 (14.4); W: 53.7 (13.9)</td>
<td>CHD (fatal and non-fatal) (ICD-9 410-414)</td>
<td>63</td>
<td>RR</td>
</tr>
<tr>
<td>Ferketich, 2000 (7,894)</td>
<td>National Health and Nutrition Examination Survey (NHANES I), USA</td>
<td>10</td>
<td>M: CES-D ≥ 16; W: CES-D ≥ 23</td>
<td>CHD (fatal and non-fatal) (ICD-9 410-414)</td>
<td>M: 49.1 (12.9); W: 46.3 (46.3) (of 7,674)</td>
<td>CHD (fatal and non-fatal) (ICD-9 410-414)</td>
<td>51.5</td>
<td>RR</td>
</tr>
<tr>
<td>Ford, 1998 (1,190)</td>
<td>The Johns Hopkins Precursors Study, USA</td>
<td>37</td>
<td>Self report of clinical depression confirmed by physician reviewers</td>
<td>CVD</td>
<td>26</td>
<td>0</td>
<td>RR</td>
<td>graduation age, baseline serum cholesterol level, premature parental MI, physical activity, time-dependent smoking, incident hypertension, incident diabetes</td>
</tr>
<tr>
<td>Haukkala, 2009 (7,933)</td>
<td>FINRISK Study, Finland</td>
<td>10-15</td>
<td>BDI quartiles</td>
<td>All CVD events (fatal and non-fatal)</td>
<td>M: 49.1 (12.9); W: 46.3 (46.3) (of 7,674)</td>
<td>All 18-20 years at baseline</td>
<td>0</td>
<td>RR</td>
</tr>
<tr>
<td>Jansky, 2010 (49,321)</td>
<td>Sweden</td>
<td>37</td>
<td>Diagnosis of psychotic or neurotic depression by psychiatrist coded to ICD-8 (296.300.4)</td>
<td>Hospitalization and mortality for CHD and AMI</td>
<td>All 18-20 years at baseline</td>
<td>0</td>
<td>HR</td>
<td>smoking, body length, diabetes, SBP, alcohol consumption, physical activity, father’s occupation, family history of CHD, geographic area</td>
</tr>
<tr>
<td>Joukamaa, 2001 (8,000)</td>
<td>Mini-Finland Health Survey, Finland</td>
<td>17</td>
<td>GHQ-36: neurotic depression</td>
<td>Cardiovascular disease mortality</td>
<td>Not given</td>
<td>54.6</td>
<td>RR</td>
<td>age</td>
</tr>
<tr>
<td>Kubzansky, 2006 (1,306)</td>
<td>Normative Aging Study, Boston USA</td>
<td>10.9 (3.3)</td>
<td>MMPI-2: iso-depression</td>
<td>CHD endpoints (angina pectoris, MI, fatal CHD)</td>
<td>61 (8.3)</td>
<td>0</td>
<td>RR</td>
<td>age, smoking status, SBP and DBP, serum total cholesterol, BMI, family history of CHD, educational attainment, alcohol intake</td>
</tr>
<tr>
<td>Nicholson, 2005 (5,449)</td>
<td>Whitehall II study, London, United Kingdom</td>
<td>6.8</td>
<td>GHQ-30 score ≥ 5</td>
<td>CHD death, non-fatal MI and angina</td>
<td>By distress group: never 49.6, persistent 47.9, new 48.3, former 49.1.</td>
<td>0</td>
<td>HR</td>
<td>smoking, SBP, DBP, cholesterol, BMI</td>
</tr>
<tr>
<td>Penninx, 1998 (3,701)</td>
<td>New Haven, East Boston, Iowa samples of the Established Populations for the Epidemiologic Studies of the Elderly (EPESE) project, USA</td>
<td>6</td>
<td>CES-D ≥ 20</td>
<td>First CVD event</td>
<td>Never depressed 78.1 (5.4), newly depressed 79.5 (5.7), chronically depressed 79.3 (5.9)</td>
<td>Never depressed 64.4%, newly depressed 73.8%, chronically depressed 83.7%</td>
<td>RR</td>
<td>age, sex, region, cigarette smoking, alcohol intake, BMI, blood pressure, history of stroke, diabetes, or cancer, physical disability</td>
</tr>
<tr>
<td>Phillips, 2009 (4,256)</td>
<td>The Vietnam Experience Study, USA</td>
<td>15</td>
<td>Diagnostic Interview Schedule (version 3A) mapped to DSM-III</td>
<td>CVD mortality (ICD-9 390-434, 436-448; ICD-10 100-178)</td>
<td>38.3</td>
<td>0</td>
<td>HR</td>
<td>age</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Location</td>
<td>Sample Size</td>
<td>Design</td>
<td>Exposure</td>
<td>Outcome</td>
<td>Risk Estimate</td>
<td>Risk Factors</td>
</tr>
<tr>
<td>-------</td>
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</tr>
<tr>
<td>Pratt, 1996</td>
<td>(1,551)</td>
<td>Baltimore cohort of the Epidemiological Catchment Area Study, USA</td>
<td>12-13</td>
<td>National Institutes of Mental Health DIS mapped to DSM-III: (1) reference group, no history of 2 weeks of dysphoria (2) history of dysphoria but never met clinical criteria for MDE (3) people who met clinical criteria for MDE at some point in their lives.</td>
<td>Self reported heart attack</td>
<td>By exposure category: (3) 35.6% aged &lt; 30 (2) 36.7% aged &lt; 30 (1) 35.7% aged &lt; 30</td>
<td>62% OR sex, age, marital status, history of hypertension</td>
<td></td>
</tr>
<tr>
<td>Salaycik, 2007</td>
<td>(4,120)</td>
<td>Framingham Heart Study, USA</td>
<td>8</td>
<td>CES-D ≥ 16</td>
<td>Incident stroke/TIA</td>
<td>63.9 (12.3)</td>
<td>56 HR age, sex, blood pressure, diabetes, atrial fibrillation, history of CVD, left ventricular hypertrophy on ECG, current smoking</td>
<td></td>
</tr>
<tr>
<td>Scherrer, 2009</td>
<td>(16,634)</td>
<td>Veterans Affairs administrative and pharmacy databases, USA</td>
<td>Not given</td>
<td>Major depression: two separate outpatient or one inpatient admission (ICD-9 296.2, 296.3, 300.4, 311).</td>
<td>Incident Ml; outpatient or inpatient with ICD-9-CM codes 410-412</td>
<td>61.3 (11.1)</td>
<td>6.8 HR gender, race, age, marital status, insurance status</td>
<td></td>
</tr>
<tr>
<td>Sesso, 1998</td>
<td>(1,305)</td>
<td>Normative Aging Study, Boston USA</td>
<td>7.0 (2.3)</td>
<td>Minnesota Multiphasic Personality Inventory MMPI-2 D clinical scale</td>
<td>CHD (non-fatal MI and fatal CHD) and angina pectoris</td>
<td>61.8 (8.3)</td>
<td>0 RR age, smoking status, SBP, DBP, BMI, family history of CHD, alcohol intake</td>
<td></td>
</tr>
<tr>
<td>Surtees, 2008a</td>
<td>(19,649)</td>
<td>United Kingdom European Prospective Investigation into Cancer - Norfolk Study, United Kingdom</td>
<td>8.5</td>
<td>Health and Life Experiences Questionnaire coded to DSM-IV criteria</td>
<td>IHD mortality Range 41-80 years</td>
<td>58 HR age, sex, cigarette smoking, SBP, total cholesterol level, physical activity, BMI, diabetes, social class, heavy alcohol use, antidepressant medication use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surtees, 2008b</td>
<td>(20,627)</td>
<td>United Kingdom European Prospective Investigation into Cancer - Norfolk Study, United Kingdom</td>
<td>8.5</td>
<td>Mental Health Inventory (MHI-5)</td>
<td>Stroke (fatal and non-fatal) Range 41-80 years</td>
<td>69 HR age, sex, smoking, SBP, total cholesterol, obesity, pre-existing MI, diabetes, social class, education, hypertension treatment, family history of stroke, antidepressant medication use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vinkers, 2004</td>
<td>(192)</td>
<td>Leiden 85-plus Study, The Netherlands</td>
<td>3.2</td>
<td>GDS-15 ≥ 4</td>
<td>Cardiovascular mortality 85 years at baseline</td>
<td>62.6 (of whole sample) RR gender, smoking, alcohol consumption, number of chronic diseases (excluding CVD)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
up period was 14 years (range 3.2–37 years).

Seven of these 12 studies found a significant positive relationship between depression and mortality from cardiovascular disease, with an overall pooled effect of 1.35 (95% confidence interval (CI): 1.17, 1.56) (Table 4). Seven papers presented data for men only and eight for women only. Only two studies revealed significant results for men; however, the overall pooled effect of 1.22 was not statistically significant (95% CI: 0.99, 1.49).

When the results were split into stroke and cardiovascular disease excluding stroke, the pooled effects were significant for mortality from CHD/AMI (1.24; 95% CI: 1.07, 1.44) but not for stroke mortality (1.28; 95% CI: 0.92, 1.78).

Fatal and non-fatal cardiovascular disease:

Twenty-four studies were included where results were published for fatal and/or non-fatal cardiovascular disease incidence (Table 5, Figure 2). These include studies presenting results for women only and cardiovascular disease excluding stroke, only the latter found a significant relationship between depression and incident cardiovascular disease (coronary

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Description</th>
<th>Follow-up Period</th>
<th>CES-D cut-off</th>
<th>Incident Cardiovascular Disease</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wassertheil-Smoller, 2004 (73,098)</td>
<td>Women’s Health Initiative Observational Study, USA</td>
<td>14 years (range 3.2–37)</td>
<td>CES-D ≥ 5</td>
<td>First occurrence of congestive heart failure, CHD (fatal or non-fatal MI), coronary artery disease (MI or coronary death, angina, CAGB, angio-plasty), stroke, CVD death</td>
<td>1.22 (1.07, 1.39)</td>
</tr>
<tr>
<td>Wulsin, 2005 (3,634)</td>
<td>Framingham Heart Study, USA</td>
<td>12</td>
<td>CES-D ≥ 16</td>
<td>Incident cases of sudden cardiac death, fatal CHD, and non-fatal MI</td>
<td>1.61 (1.27, 2.04)</td>
</tr>
<tr>
<td>Wouts, 2008 (2,965)</td>
<td>Longitudinal Aging Study Amsterdam (LASA), The Netherlands</td>
<td>7.7 (3.1)</td>
<td>CES-D ≥ 16</td>
<td>Stroke</td>
<td>1.85 (1.42, 2.41)</td>
</tr>
<tr>
<td>Whang, 2009 (63,469)</td>
<td>The Nurses’ Health Study cohort, USA</td>
<td>5.9</td>
<td>CES-D ≥ 16</td>
<td>Hard CHD incidence: MI and CHD death</td>
<td>1.82 (1.50, 2.20)</td>
</tr>
</tbody>
</table>

BDI = Beck Depression Inventory; BMI = body mass index; CES-D = Center for Epidemiological Studies Depression Scale; CHD = coronary heart disease; DBP = diastolic blood pressure; DIS = Diagnostic Interview Schedule; DSM = diagnostic and statistical manual of mental disorders; ECG = electrocardiogram; GHQ = General Health Questionnaire; GWB-D = General Well-Being Schedule Depression; GDS = Geriatric Depression Scale; HR = hazard ratio; ICD = International Classification of Diseases; M = men; MDE = major depressive episode; MI = myocardial infarction; MMPI = Minnesota Multiphasic Personality Inventory; MMSE = mini-mental state examination; OBS = Obvious Depression Scale; OR = odds ratio; RH = relative hazard ratio; RR = relative risk; SBP = systolic blood pressure; SD = standard deviation; TIA = transient ischemic attack; USA = United States of America; W = women.
Table 2. Characteristics of included studies with continuous exposure variable.

<table>
<thead>
<tr>
<th>Study: first author, year (no. of subjects)</th>
<th>Study name (source)</th>
<th>Observation period, years (SD)</th>
<th>Depression measure</th>
<th>Outcome measure</th>
<th>Mean age, years (SD)</th>
<th>Proportion female (%)</th>
<th>Risk type</th>
<th>Factors adjusted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ariyo, 2000 (4,493)</td>
<td>Cardiovascular Health Study, USA</td>
<td>6</td>
<td>CES-D</td>
<td>CHD: first occurrence of angina, MI, angioplasty, CABG, or coronary death</td>
<td>M: 73; W: 72</td>
<td>61</td>
<td>HR</td>
<td>age, race, sex, education, diabetes, hypertension, smoking status, physical activity, physical inactivity, total cholesterol, physical inactivity, marital status, alcohol consumption, time-dependent covariate for angina</td>
</tr>
<tr>
<td>Barefoot, 1996 (679)</td>
<td>Glostrup, Denmark</td>
<td>27</td>
<td>MMPI 40-item OBD</td>
<td>AMI (fatal and non-fatal)</td>
<td>All 50 years old in 1964 and 60 years old in 1974</td>
<td>44% of original 730 participants</td>
<td>RR</td>
<td>age, sex</td>
</tr>
<tr>
<td>Boyle, 2006 (2,105)</td>
<td>Air Force Health Study (AFHS), USA</td>
<td>18</td>
<td>MMPI 40-item OBD</td>
<td>Incident CHD</td>
<td>46.7 (7.6)</td>
<td>0</td>
<td>HR</td>
<td>age, total cholesterol, smoking status, hypertensive status, diabetes status, HDL cholesterol, BMI</td>
</tr>
<tr>
<td>Davidson, 2009 (1,794)</td>
<td>The 1995 Nova Scotia Health Survey (NSHS95), Canada</td>
<td>10</td>
<td>CES-D</td>
<td>Incident CHD including mortality</td>
<td>46.3 (18.3)</td>
<td>50</td>
<td>HR</td>
<td>sex, gender, Framingham risk score</td>
</tr>
<tr>
<td>Kamphuis, 2009 (909)</td>
<td>Finland, Italy, and the Netherlands Elderly (FINE) Study; Finland, Italy &amp; The Netherlands</td>
<td>10</td>
<td>Zung Self-rating Depression Scale</td>
<td>Mortality from CVD: ICD-9 (390-459)</td>
<td>By depressive symptoms: low 75.7 (4.2); middle 76.5 (4.5); high 77.1 (4.9)</td>
<td>0</td>
<td>HR</td>
<td>age, country, years of education, living alone, physical activity</td>
</tr>
<tr>
<td>Mausbach, 2007 (643)</td>
<td>Resources for Enhancing Alzheimer's Caregiver Health (REACH) project, USA</td>
<td>1.5</td>
<td>CES-D</td>
<td>Onset of heart disease</td>
<td>56.7 (13.2)</td>
<td>85</td>
<td>RR</td>
<td>age, sex, ethnicity, years of education, years of caregiving, current smoking status, high blood pressure, self-rated health, taking antidepressant medication, whether or not caregiver provided 9 or more hours of care per day, whether or not the caregiver was assigned to an active REACH treatment condition</td>
</tr>
<tr>
<td>Wulsin, 2005 (3,634)</td>
<td>Framingham Heart Study, USA</td>
<td>5.9</td>
<td>CES-D</td>
<td>Hard CHD incidence: MI and CHD death</td>
<td>CES-D &lt; 16: 53 (14); CES-D ≥ 16: 50 (13)</td>
<td>CES-D &lt; 16: 53% CES-D ≥ 16: 68%</td>
<td>RR</td>
<td>sex, age, smoking, hypertension, diabetes, BMI, total cholesterol, alcohol consumption</td>
</tr>
</tbody>
</table>

AMI = acute myocardial infarction; BMI = body mass index; CABG = coronary artery bypass graft; CES-D = Center for Epidemiological Studies Depression Scale; CHD = coronary heart disease; CVD = cardiovascular disease; HR = hazard ratio; M = men; MI = myocardial infarction; MMPI = Minnesota Multiphasic Personality Inventory; OBD = Obvious Depression Scale; RR = relative risk; SD = standard deviation; USA = United States of America; W = women.

heart disease, acute myocardial infarction or angina; 1.30, 95% CI: 1.18, 1.45).

Non-fatal cardiovascular disease: Seven studies were included where results were published for non-fatal cardiovascular disease (coronary heart disease, acute myocardial infarction, angina, and stroke) (Table 6). This includes studies where medical records were used to ascertain incident cardiovascular disease. A significant pooled effect was found for any type of incident cardiovascular disease (1.38, 95% CI: 1.16, 1.64). In this case the result remained significant for men (1.60, 95% CI: 1.22, 2.08) but not women (1.16, 95% CI: 0.92, 1.46). Only one study was included where non-fatal stroke could be separated from fatal stroke. **Self-reported cardiovascular disease:** Only four studies were included where incident cardiovascular disease was self-reported (Table 7). The pooled estimate for the relationship between depression and self-reported coronary heart disease (including acute myocardial infarction and angina) was not significant (1.49, 95% CI: 0.93, 2.37).
Studies with continuous exposure variable:
Seven studies used a continuous exposure variable (Figure 3). Five of these studies found a significant positive relationship between depression and incident cardiovascular disease (non-fatal and fatal). The overall pooled effect of 1.15 was statistically significant (95% CI: 1.06, 1.25).

Sensitivity analysis:
Analyses were undertaken excluding the lowest quality studies (those scoring less than five points on the quality assessment).

Exclusion of five studies from the analysis of depression and all cardiovascular disease mortality reduced heterogeneity from 84% to 68% and caused the pooled estimate to become non-significant (changing from 1.35 (95% CI: 1.17, 1.56) to 1.36 (95% CI: 0.96, 1.93)).

Exclusion of eight studies from the analysis of depression and all cardiovascular disease (fatal and non-fatal) reduced heterogeneity from 74% to 53% and decreased the pooled estimate from 1.30 (95% CI: 1.19, 1.43) to 1.28 (95% CI: 1.12, 1.46).

Of the seven studies which published stroke as an outcome (Table 5), only three scored five or more points in the quality assessment. These remaining studies resulted in a pooled estimate of 1.01 (95% CI: 0.81, 1.27) as compared to 1.12 (95% CI: 0.95, 1.33) using all seven studies.

Discussion

This study extends the body of evidence demonstrating that depression during adult life is a predictor for incident cardiovascular disease—both fatal and non-fatal. This meta-analysis expands on earlier work done by Van der Kooy et al. (8); it updates the literature, and to our knowledge is unique in allowing studies using medical records to be included in the analysis. Previous research has been limited by the inclusion of existing cardiovascular disease, which is an important confounding variable. This review addressed this by excluding studies where participants had pre-

<table>
<thead>
<tr>
<th>Table 3. Quality assessment.</th>
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<tbody>
<tr>
<td>Study</td>
</tr>
<tr>
<td>Bremmer, 2006</td>
</tr>
<tr>
<td>Whang, 2009</td>
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<tr>
<td>Ariyo, 2000</td>
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<tr>
<td>Boyle, 2006</td>
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<tr>
<td>Davidson, 2009</td>
</tr>
<tr>
<td>Kubzansky, 2006</td>
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<tr>
<td>Mausbach, 2007</td>
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<tr>
<td>Pratt, 1996</td>
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<tr>
<td>Sesso, 1998</td>
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<tr>
<td>Wassertheil-Smoller, 2004</td>
</tr>
<tr>
<td>Ferketich, 2000</td>
</tr>
<tr>
<td>Haukkala, 2009</td>
</tr>
<tr>
<td>Jansky, 2010</td>
</tr>
<tr>
<td>Kamphuis, 2009</td>
</tr>
<tr>
<td>Nicholson, 2005</td>
</tr>
<tr>
<td>Pennix, 1998</td>
</tr>
<tr>
<td>Surtees, 2008a</td>
</tr>
<tr>
<td>Surtees, 2008b</td>
</tr>
<tr>
<td>Wouts, 2008</td>
</tr>
<tr>
<td>Wulsin, 2005</td>
</tr>
<tr>
<td>Empana, 2006</td>
</tr>
<tr>
<td>Everson, 1998</td>
</tr>
<tr>
<td>Ford, 1998</td>
</tr>
<tr>
<td>Joukamaa, 2001</td>
</tr>
</tbody>
</table>
existing cardiovascular disease of the same type as the study outcome and this was not adjusted for. Pooled estimates found that compared to people free of depression, those with depression were 35% more likely to suffer a fatal cardiovascular event, 30% more likely to experience a fatal or non-fatal cardiovascular event, and 38% more likely to develop non-fatal cardiovascular disease.

Sub-analysis of the relationship between depression and cardiovascular mortality and/or morbidity was significant for CHD/AMI/angina but not for stroke, although the pooled estimates for mortality were similar (1.24 for CHD/AMI and 1.28 for stroke).

Interestingly, the pooled estimate for the increased risk of experiencing a fatal coronary heart disease event or acute myocardial infarction for depressed men was much greater than for depressed women (1.85 for men and 1.09 for women). The result for men was subject to substantial heterogeneity (90%) while that for women was 0%. Despite this, each result was robust in sensitivity analysis. Therefore, it may be that the effect of depression is greater for men than for women. This may be due to factors such as the time-course of depression, its severity, treatment patterns, physiological differences, or other unknown mechanisms.

Comparison with other meta-analyses:
Previous meta-analyses have found relatively comparable relationships between depression and the risk of developing cardiovascular disease. Wulsin et al. (43) found a 64% combined overall increased risk of the onset of coronary disease in people with depression compared to those without. Their study specifically required incidence of coronary disease in addition to deaths, and did not include stroke.

The National Heart Foundation of Australia published a position statement citing evidence that there is “strong and consistent” evidence for depression as an independent risk factor for coronary heart disease, with the strength of association being comparable to cigarette smoking or hypercholesterolaemia (44).

A more recent study by Van der Kooy et al. (8) found that depressed mood increased the risk for cardiovascular disease, including myocardial infarction, coronary heart disease and stroke. The pooled effect size for all included studies was 1.46 (95% CI: 1.37, 1.55). Their analysis did

Table 4. Statistical pooling—mortality only

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of studies</th>
<th>Pooled effect size</th>
<th>95% CI</th>
<th>I² (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any CVDb,c</td>
<td>12</td>
<td>1.35</td>
<td>1.17, 1.56</td>
<td>84</td>
</tr>
<tr>
<td>Any CVD – malesc</td>
<td>7</td>
<td>1.61</td>
<td>1.02, 2.54</td>
<td>78</td>
</tr>
<tr>
<td>Any CVD – femalesc</td>
<td>8</td>
<td>1.22</td>
<td>0.99, 1.49</td>
<td>83</td>
</tr>
<tr>
<td>Strokea</td>
<td>3</td>
<td>1.28</td>
<td>0.92, 1.78</td>
<td>na</td>
</tr>
<tr>
<td>CHD/AMIF</td>
<td>5</td>
<td>1.24</td>
<td>1.07, 1.44</td>
<td>79</td>
</tr>
<tr>
<td>CHD/AMI – malesc</td>
<td>4</td>
<td>1.85</td>
<td>1.07, 3.22</td>
<td>90</td>
</tr>
<tr>
<td>CHD/AMI – femalesd</td>
<td>5</td>
<td>1.09</td>
<td>1.02, 1.15</td>
<td>0</td>
</tr>
</tbody>
</table>

AMI = acute myocardial infarction; CHD = coronary heart disease; CI = confidence interval; CVD = cardiovascular disease; I² = heterogeneity statistic; na = not applicable.

Table 5. Statistical pooling—mortality and/or morbidity (any data source)

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of studies</th>
<th>Pooled effect size</th>
<th>95% CI</th>
<th>I² (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any CVDb,c</td>
<td>24</td>
<td>1.30</td>
<td>1.19, 1.43</td>
<td>74</td>
</tr>
<tr>
<td>Any CVD for malesb,c</td>
<td>12</td>
<td>1.37</td>
<td>1.14, 1.66</td>
<td>63</td>
</tr>
<tr>
<td>Any CVD for femalesb,c</td>
<td>9</td>
<td>1.18</td>
<td>1.04, 1.35</td>
<td>76</td>
</tr>
<tr>
<td>Strokea</td>
<td>7</td>
<td>1.12</td>
<td>0.95, 1.33</td>
<td>48</td>
</tr>
<tr>
<td>Stroke in femalesd</td>
<td>3</td>
<td>1.01</td>
<td>0.80, 1.27</td>
<td>na</td>
</tr>
<tr>
<td>CHD/AMI/anginab</td>
<td>15</td>
<td>1.30</td>
<td>1.18, 1.45</td>
<td>71</td>
</tr>
</tbody>
</table>

AMI = acute myocardial infarction; CHD = coronary heart disease; CI = confidence interval; CVD = cardiovascular disease; I² = heterogeneity statistic; na = not applicable.

A = all pre-existing cardiovascular diseases excluded from study or final analysis; B = depression measured through a validated questionnaire; C = control for anti-depressant medication; D = follow-up of 10 years or more (median of studies); E = sample size of 1,000 or more; F = medical records not used as sole/primary source of outcome; G = basic demographic information (age, sex) given for final study population; H = adjusted risk estimates published; + = meets criterion; - = does not meet criterion; ? = indeterminate.

a First author, year.

b Quality score, total “+”.

c Analysed using random effects.

d Analysed using fixed effects.
AMJ = acute myocardial infarction; CAD = coronary artery disease; CHD = coronary heart disease; CVD = cardiovascular disease; F = fatal; GE65 = people aged 65 years and over; LT65 = people aged less than 65 years; M = men only; NF = non-fatal; W = women only; Str = stroke.

Table 6. Statistical pooling—morbidity only (any data source)\(^a\)

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of studies</th>
<th>Pooled effect size</th>
<th>95% CI</th>
<th>I(^2) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any CVD(^{b,c})</td>
<td>7</td>
<td>1.38</td>
<td>1.16, 1.64</td>
<td>44</td>
</tr>
<tr>
<td>Any CVD for males(^{b,c})</td>
<td>5</td>
<td>1.60</td>
<td>1.22, 2.08</td>
<td>0</td>
</tr>
<tr>
<td>Any CVD for females(^{b,c})</td>
<td>3</td>
<td>1.16</td>
<td>0.92, 1.46</td>
<td>na</td>
</tr>
<tr>
<td>Stroke(^{b,c})</td>
<td>1</td>
<td>1.18</td>
<td>0.70, 1.98</td>
<td>na</td>
</tr>
<tr>
<td>CHD/AMI/angina(^{b,c})</td>
<td>6</td>
<td>1.41</td>
<td>1.18, 1.70</td>
<td>49</td>
</tr>
</tbody>
</table>

AMI = acute myocardial infarction; CHD = coronary heart disease; CI = confidence interval; CVD = cardiovascular disease; F = heterogeneity statistic; na = not applicable.

\(^a\) Studies with dichotomous or categorical depression measure only.

\(^b\) Any CVD includes cerebrovascular disease/stroke.

\(^c\) Analysed using fixed effects.

Table 7. Statistical pooling—morbidity only (self-reported data)\(^b\)

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of studies</th>
<th>Pooled effect size</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD/AMI(^c)</td>
<td>4</td>
<td>1.49</td>
<td>0.93, 2.37</td>
</tr>
</tbody>
</table>

AMI = acute myocardial infarction; CHD = coronary heart disease; CI = confidence interval; F = heterogeneity statistic.

\(^b\) One study included confirmation of self-reported CVD through medical records.

\(^c\) Studies with dichotomous or categorical depression measure only.

\(^c\) Analysed using random effects.

AMI = acute myocardial infarction; CHD = coronary heart disease; CVD = cardiovascular disease; F = fatal; GE65 = people aged 65 years and over; LT65 = people aged less than 65 years; M = men only; NF = non-fatal; W = women only; Str = stroke.

Figure 2. Forest plot of depression (comparison) as a risk factor for any cardiovascular disease, fatal and nonfatal (outcome).

Figure 3. Forest plot of depression on continuous scale (comparison) as a risk factor for any cardiovascular disease, fatal and nonfatal (outcome).

not attempt to screen out pre-existing cardiovascular disease, however, they did include analysis of cardiovascular disease free populations, which resulted in a pooled effect of 1.57 (95% CI: 1.36, 1.81). Our study did not yield any statistically significant results for stroke alone (mortality and/or morbidity), while Van der Kooy et al. calculated a pooled estimate for the increased risk of stroke in depressed persons as 1.43 (95% CI: 1.29, 1.69). Our analysis of stroke explicitly excluded studies where participants had previously experienced stroke, whereas Van der Kooy et al. did not.

**Biological basis for depression as a risk factor for cardiovascular disease:** Depression can increase the risk of developing cardiovascular disease indirectly through its influence on behaviour. Increased smoking and decreased physical activity are more common in people with depression (45-46) and increase the risk of developing cardiovascular disease. Psychosocial factors such as depression may increase the risk of developing atherosclerosis directly by damaging endothelium or exacerbating biomedical risk factors such as hypertension and dyslipidaemia (47).

Direct mechanisms by which depression may increase the risk of cardiovascular disease include autonomic dysregulation and increased expression of inflammatory bio-markers (such as C-reactive protein and Interleukin-6) (48-49). Interestingly, in their meta-analysis Howren et al. (50) found significant associations between depression and the inflammatory markers C-reactive protein, Interleukin-1 and Interleukin-6, however, they note that the relationship may be bi-directional.

Depression can lead to activation and abnormal feedback to the hypothalamic-pituitary-adrenal axis, which can then lead to cardiac dysfunction (48).

**Limitations:**
The results of any meta-analysis should be
interpreted with caution. It is possible that by only using PubMed to search for articles, and limiting these to papers with abstracts, that some studies were missed. Restricting the papers to those in English has the potential to bias the results if studies published in other languages (and possibly on different populations) report different findings. Publication bias may also influence the studies available for analysis. Figures 4 to 6 show funnel plots for the studies included in this meta-analysis. Figure 4—showing the funnel plot for studies reporting depression categorically—shows a reasonable degree of symmetry, however there is a slight outlier point represented by Wouts et al. (41). Removing this study reveals reasonably symmetrical distribution with only a slight rightward deviation (Figure 5), and has a negligible effect on the pooled estimate. Figure 6—showing the funnel plot for studies reporting depression on a continuous scale—shows a slight rightward bias, but again removing the two most extreme studies (Barefoot & Schroll (19) and Davidson et al. (21)) has only a minor effect on the pooled estimate (reduced from 1.14 to 1.11).

Despite the attempt to apply rigorous selection criteria, there will always be heterogeneity in the approaches and classifications used by different studies. Sources of heterogeneity include: the demographics of study populations; assessment and classification of the exposure variable, depression; assessment and classification of the outcome variables, cardiovascular disease; and length of follow up. Some of these are discussed below.

Most of the included studies were undertaken in the United States of America and Western Europe. While these are relatively wealthy populations, their peoples are likely to have variable access to health care within and between countries (51). Furthermore, people of different ethnic backgrounds will have different genetic risk profiles for developing cardiovascular disease (52).

A wide range of tools were used for assessing and classifying depression, which is likely to be a significant contributor to heterogeneity. Where exposure was categorised to more than three categories, the most depressed participants were compared against the non-depressed participants, which is likely to increase any observed relationship between depression and cardiovascular disease.

Medical records were used by many studies to ascertain cardiovascular incidence. These will necessarily be biased towards more serious cases (that is, those requiring hospitalisation or resulting in a death). Use of medical records alone has the potential to miss many incident cases of cardiovascular disease, such as cases not requiring hospital admission and those where the hospitalisation occurred in a hospital from which data was not collected.

The length of follow-up varied from 3.2 years (38) to 37 years (5, 24). This paper could not assess the exposure time required to see an effect of depression on cardiovascular incidence, but it is likely that longer exposure will increase the risk of developing disease.

Although considerable heterogeneity was reported in some analysis, the findings of this meta-analysis were consistent and robust in sensitivity analyses. These were also based on large numbers of participants and represent the most comprehensive synthesis of data available on the link between depression and cardiovascular disease.

Data extraction and quality assessment was undertaken by KO. All care was taken to review data extraction for accuracy on initial extraction and on at least two subsequent occasions for each included study.

The protocol for this review was not published before undertaking the study.

**Recommendations for future research:**
The evidence for depression as an independent risk factor for cardiovascular disease is compelling. More research into biological mechanisms behind this
relationship could lead to a better understanding of how to manage or treat the cardiovascular effects of depression. Research comparing the risks for different types of cardiovascular disease (e.g., coronary heart disease, stroke) and different types of stroke (ischaemic versus haemorrhagic) would be of value. Some antidepressant medications can have adverse cardiovascular effects (53-54). Davidson et al. (54) found that antidepressant use was associated with increased incidence of stroke and cardiac death, while Marano et al. (55) suggest that selective serotonin reuptake inhibitors, which they state are not associated with adverse cardiovascular outcomes, should be used in preference to tricyclic antidepressants in patients with co-morbid depression and cardiovascular disease. More research is needed into the safety of different classes of antidepressants in people with cardiovascular disease, and whether their use can mitigate the cardiovascular effects of depression in people with and without pre-existing cardiovascular disease. Similarly, more studies into the impact of non-pharmacological treatments for depression such as cognitive behavioural therapy on both depression and co-morbid conditions should be conducted.

Finally, further research into which population sub-groups are at particular risk of depression and developing subsequent cardiovascular disease—for example, men compared to women, younger people compared to older people—and quantification of the impact of the duration of exposure would be of benefit.

Conclusion

This study has contributed to research identifying depression as a risk factor for developing cardiovascular disease. Importantly, this study attempted to exclude people with pre-existing cardiovascular diseases from the analysis, so as to capture incident non-fatal as well as fatal cardiovascular disease, and therefore produce a more robust estimate of the effect size of depression on the incidence of cardiovascular disease. This study reinforces that clinicians need to be aware that treating depression is important not only for relieving the symptoms of depression itself, but for reducing the risk of developing cardiovascular disease which has high morbidity and mortality, and for moderating the progression of cardiovascular disease.

References:

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52. Institute of Genetic Medicine, Medicine JH. Online Mendelian Inheritance in Man. [Internet]. Institute of Genetic Medicine; 2011 [cited 2011 Aug 14]; Available from: http://omim.org/
Smartphones: friend or fomite?

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With the explosive proliferation of mobile phone applications improving clinical information flow, the smartphone is rapidly becoming the new indispensable tool of hospital medicine (3). In response to this rapid change in professional culture, the safety of smartphones in the clinical setting has been viewed with interest, in particular their potential for transmission of nosocomial infection. As with other fomite research, practicable clinical evidence remains elusive, as do consistent clinical guidelines. Nevertheless, understanding the scope of current evidence and strategies for risk minimisation remains important moving forward into a future of smartphone use in daily practice.

Ubiquitous and indispensable

Over the past decade, the diversity of phone-based tools in healthcare has evolved from enabling responsive communication between colleagues, exchanging images at the bedside and replacing the traditional pocket handbook, to encompass clinical data collection, ongoing education, infectious disease reporting, patient results notification and chronic disease monitoring (4,5). More utility emerges daily, the development seemingly exponential. Enormous potential for health promotion has just begun to be explored (6) and undoubtedly medical applications employing augmented reality are just over the horizon (7). Indeed the role of the smartphone has already been cemented, ironically at the opposite end of the technology spectrum. Thanks to ‘bare below the elbows’ policies in many hospitals resulting in the phasing out of wristwatches (8), the vital accessory status of the mobile phone has been all but assured – if only to keep time and take pulses at the bedside (3).

Concerns for patient safety

Despite smartphone popularity, concerns of patient safety have been raised regarding electromagnetic interference, patient confidentiality, stored data security, noise disruption and distraction within the clinical environment (9-11). In particular, compelling evidence demonstrates that mobile phones act as a reservoir for bacteria known to cause nosocomial infections (10,12-14). With increasing mobile medical software use amongst new cohorts of medical graduates and junior doctors (5), smartphones present an emerging potential risk of cross-contamination between health care workers (HCWs), inpatients and the community (3,13).

Personal smartphone use in daily practice overtakes historical scrutiny of the infection potential posed by consultant’s personal digital assistants (PDAs) and hospital-property pagers. Unger et al. and other authors have suggested the important and growing threat to public health, particularly in developing counties (15), drawing on urgent and evocative metaphor to aid effect, describing the potential for mobile phones to act as “Trojan horses” in the transmission of infection (16). Contrastingly, other authors have expressed only minimal concern, arguing that phones are simply an extension of the hands - as distinct from tools that have direct patient contact - and are therefore addressed in the presence of a strict hand hygiene routine to interrupt transmission (17).

Contamination studies

The first study of microbial contamination of mobile phones was conducted in a tertiary hospital in Israel in 2002, in which 124 physicians’ and nurses’ phones were cultured for Acinetobacter (18). In the past decade, several further studies have examined the microbial contamination of mobile phones (13,15,16,19-21). A systematic review in 2009 by Brady et al. identified 14 studies of mobile phones between 2005 and 2009, ranging in sample size from 30 to 400 phones (10). No larger studies having been conducted since.

The largest study conducted to date involved a cohort of 400 hospital HCWs and 100 community controls across 4 tertiary centres in USA and Israel and across departments with heavy patient contact. It showed 10-38% of the cellular telephones that belonged to HCWs harbored potentially pathogenic microorganisms. Around half the HCWs reported mobile phone use during patient contact (38-58%), and those who reported doing so showed significantly higher rates of contaminated phones compared to those who did not. Amongst the control group, all of the phones that owners reported had never entered a hospital were free from potentially pathogenic contamination (16).

Fomite of the month?

The numbers may be alarming, however researchers admit “you will find infectious organisms on everything if you test for them” (17). The weakness of contamination study evidence is the inability to answer the key question of clinical significance: what is the real world infection risk posed to patients from contaminated smartphones?

Fomites are an age-old problem. Placed in context, smartphones can be viewed as simply the current forerunner of a tedious lineage of contamination studies. Microbes have been cultured from all manner of personal and clinical equipment: from pens (22,23), pagers (10); stethoscopes (24,25), and patient notes (26); to keyboards (27), bathroom taps, door handles (27,28) and bed remotes (29); to ultrasound probes (30), ECG wires (31), blood pressure cuffs (32,33), venesection tourniquets (34), and adhesive tape (35). You may not think too hard about your change from lunch at the cafeteria, but someone has (36). One study even cultured hand sanitizer dispensers, with disturbing results (37).
Like their historical predecessors, the role of smartphones in onward transmission of infection has not been adequately assessed (3,10,13), with the inherent difficulty of reliably isolating causality posing a major barrier to such studies. Lacking clinical evidence, the bottom line remains that the infection risk posed by mobile phones may be no different to that presented by stationary telephones in the hospital (18).

Absence of guidance
In response, common sense should prevail – however this too appears to be lagging behind. While strict adherence to changing clothes, removing jewelry, covering hair and rigorous hand hygiene measures has been enacted to limit the transfer of potentially harmful bacteria from the external clinical environment into the operating environment, most hospitals place no specific restriction on the use of mobile phones in clinically sensitive areas (20).

Authors consistently draw attention to the lack of coherent guidelines for HCWs around how to prevent the cross-contamination of mobile phones (10,38). Many propose that surface disinfection recommendations be developed and added to hospital infection control policies (13,39,40), while some have gone as far as to suggest strict policies restricting their use in the clinical setting and mandating cleaning between each patient encounter (11).

For better or worse in the eyes of clinical staff, hospital guidelines remain forthcoming – leaving the immediate decision to respond a personal one.

Effective solutions
Reinforcement of strict hand hygiene policy implementation remains the cornerstone of mobile phone contamination prevention (10).

Regular disinfection of mobile phones with antiseptic surface wipes has been shown to effectively reduce contamination (10,14), one researcher going as far as to visually demonstrate the fact by pressing microbiology students’ phones into plates of agar before and after cleaning (41). The recommended antiseptic regimen is less clear.

In a study comparing decontaminating agents for pagers, chlorhexidine-alcohol wipes were recommended as the most efficacious, above alcohol-only wipes in reducing bacterial load (42). However another study comparing surface decontamination found that wiping surfaces three times reduced bacterial counts by over 80% more than one wipe; and that all agents wiped thrice - including simple saline - proved equally efficacious (43). Confounding advice for all chemical agents, is the fact that some phone manufacturers advise against use of cleaning fluids (38). As an adjunct solution, wipe-
clean phone covers have been suggested (8).

Alternatively seeking technical solutions, several authors have recommended further studies into medical-specific antibacterial covers made of metal or silver nanotechnology, or investment in UV-light sanitising phone chargers (16, 44). However Brady et al. warns that that with such innovation, hand hygiene and phone cleaning procedures risk being downgraded as a consequence.

**Take home message**

For the time being, decontamination remains optional for hospital staff – with 80% of mobile phones, pagers and PDAs never cleaned by their owners (20). As an “extension of the hands”, public perception of mobile phone hygiene in the clinical setting may be an important consideration (8), however ultimately the individual practitioner’s lingering concern for personal risk is perhaps the best incentive for a change in practices.

Unlike any other hospital instrument, the smartphone is the only one that is equally a clinical tool and personal accessory. With smartphone is the only one that is equally a clinical tool and personal accessory. With smartphones are changing the face of mobile communication safely in health care settings. Nurt Womens Health. 2013. Feb-Mar;17(1):59-62.


Does DNA PCR from placental swabs provide more information than routine placental cultures?

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Abstract

OBJECTIVES: To compare standard microbiological culture and nucleic acid-based techniques (NABT) in the identification of bacteria from placental swabs and neonatal blood of premature deliveries; and to compare the culture and NABT results with histological assessment of the placenta.

METHODS: Women and neonates delivering after spontaneous preterm labour (<37 weeks gestation) were enrolled. Placentas were assessed histologically for chorioamnionitis and funisitis. Placental swabs and neonatal blood samples were taken for routine culture and universal bacterial detection using 16S rRNA PCR.

RESULTS: Forty-six neonates were enrolled, median gestation 32 weeks and birth weight 1800 grams. 87% of women received antibiotics prior to delivery. Placental swabs were culture positive in 11% of cases and 16S rRNA PCR positive in 9% of cases (1 case was culture and PCR positive). Evidence of placental inflammation was present in 19% of the samples. Only three of the nine placenta with inflammation were culture and/or PCR positive. There was no relationship between the neonatal blood inflammatory markers, placental histology, culture, and PCR results.

CONCLUSION: In a population with low positive placental culture results 16S rRNA PCR of placental swabs does not significantly increase the identification of bacteria potentially associated with preterm delivery.

Introduction

Premature birth (less than 37 weeks gestation) occurs in up to 12% of deliveries and occurs in 1% of pregnancies less than 28 weeks gestation (1). Two-thirds of premature deliveries are associated with preterm labour or preterm premature rupture of membranes (2-4). Histological chorioamnionitis is found in up to 50% of spontaneous preterm deliveries (5) and has been implicated as a risk factor for cerebral palsy (6).

There is clinical, microbiological and epidemiological evidence associating infection and inflammation with preterm birth (7-11). Current practice to detect in-utero infection is to swab the placental surface following delivery and culture for aerobic and anaerobic bacteria. However, despite evidence of chorioamnionitis, the positive culture rate is low (12). This may reflect that culture conditions utilised are not suitable to recover the diverse organisms potentially associated with preterm birth. Recently an association has been made between periodontal infections and preterm birth (13-16). The oral cavity has a very diverse microflora with estimates that approximately only 50% is culturable (17). Furthermore, antibiotics, considered standard treatment in preterm rupture of membranes that delays delivery and reduces neonatal morbidity (18-19), will also reduce recovery of the organisms involved.

Development of a culture-independent approach involving polymerase chain reaction (PCR) amplification of bacterial DNA from easily obtainable fetal and maternal clinical samples, could improve the ability to identify infection as a cause of preterm birth. Culture-independent approaches, using PCR to amplify the bacterial gene for the 16S ribosomal RNA, referred to here as the 16S rRNA gene, have been utilised to detect and identify organisms in a range of clinical samples including amniotic fluid (20-24), and fetal membranes and/or placental tissue (25-27). All bacteria have multiple copies of the 16S rRNA gene that is comprised of (i) conserved regions, against which PCR primers can be designed to amplify this gene from diverse taxonomic groups, and (ii) variable regions, the sequence of which are species-specific enabling identification of the bacteria detected. This universal bacterial 16S rRNA PCR approach has identified a relatively diverse microflora from the clinical specimens obtained from both preterm and term pregnancies, including
unculturable bacteria that play a role in periodontal disease (21, 23, 24, 26). Amniocentesis, however, presents risks to both the mother and fetus, the major risk being fetal loss with rates reported between 0.13% to 2.2% (28). One possible limitation in working with placental tissue is the presence of inhibitors and/or DNA degrading enzymes that can prevent the detection of bacterial DNA (27). Placental swabs and neonatal blood are routinely collected postpartum and could also be used for 16S rRNA analysis without the limitations and risks involved with these other clinical specimens.

The aims of this study were to compare the ability of culture and 16S rRNA PCR to detect and identify bacteria in swabs of placentas obtained from preterm births, and to determine if the presence of bacteria is related to placental histopathology and neonatal inflammatory markers.

Materials and Methods

Women and neonates with spontaneous preterm labour (less than 37 weeks gestation) with or without prolonged rupture of membranes (greater than 24 hours) were enrolled into the study. Exclusion criteria included: elective preterm deliveries due to maternal or fetal reasons (e.g. preeclampsia, growth restriction); neonates with identified chromosomal or congenital anomalies; or fetal death in-utero. Written consent of the mother prior to or soon after delivery. The study was approved by the local Human Research Ethics Committees.

The following data were collected: maternal age, gravidity, parity, plurality, gestation in weeks (determined by early pregnancy ultrasound or fetal death in-utero). Written consent of the mother prior to or soon after delivery. The study was approved by the local Human Research Ethics Committees.

Placenta Histology

After removal of the retroplacental blood clot, the placenta was placed in 10% buffered formalin saline fixative for 48 hours. The point of rupture of the membranes was identified where possible. The membranes were stripped, by cutting them at their point of attachment to the disc. Using the point of rupture as the start, a “swiss roll” preparation of the membranes was made. The rolled membrane preparation was sampled in the transverse plane, thereby ensuring that the point of rupture was sampled. Two samples were submitted for histology. The umbilical cord was measured and samples were taken from the placental and neonatal end of the specimen. Serial sections (1 cm apart) were made of the placental disc. Samples of the placenta were submitted for histology from the periphery and central zones, as well as from any abnormal areas. These blocks included the decidual and fetal surface, in continuity, if possible. Microscopy included grading of chorioamnionitis and funisitis using the definitions of Naeye (29) and Lewis and Perrin (30).

Placental Swabs

Placentas were swabbed with sterile cotton swabs (Medical Wire & Equipment) in the delivery suite according to protocol (www.wch.sa.gov.au) and sent to microbiology for bacterial and fungal cultures, with viral cultures requested only if specifically indicated. Swabs were cultured as follows: streaked onto horse blood agar and chocolate agar and incubated at 35°C in a CO2 cabinet for 7 days; streaked onto anaerobic agar and incubated at 35°C in a container under anaerobic conditions (AnaeroGen sachet, Oxoid, Thebarton, Australia) for 3 days; and inoculated into Brain Heart Infusion broth and incubated at 35°C for 3 days, and subcultured if turbid. A second placental swab was taken and frozen at -80°C for 16S rRNA analysis. Placental swabs were taken from two healthy elective caesarean section deliveries at term for control specimens.

Neonatal Blood Sample

A full blood count (FBC), C-reactive protein (CRP) and blood culture were taken in the majority of cases due to the risk of early neonatal infection as a result of pre-mature delivery. A further 1.0 ml of blood was collected into a sterile non-heparinised tube and stored at -80°C for subsequent 16S rRNA analysis.

16S rRNA PCR technique

The frozen swabs were thawed, 1 mL of TN150 (10 mM Tris-HCl, 150 mM NaCl, pH 8) was added, and the mixture vigorously vortexed for 2 minutes. The liquid was pipetted from the swab into a new sterile 2mL screw-cap tube and centrifuged at 14,600xg for 3 minutes. The supernatant was carefully removed from the pelleted bacteria. The swab was washed two more times with 1 mL of TN150 with the bacteria pelleted in the same tube each time. DNA was extracted using Bacterial Protocol D of the QIAamp DNA Mini Kit following the manufacturer’s directions (Qiagen) and DNA was eluted in 50µL of buffer AE. DNA was extracted from cord blood using Bacterial Protocol D of the QIAamp DNA Mini Kit (Qiagen) with the following modifications: the cord blood was not centrifuged prior to the addition of lysozyme, and the DNA was eluted in 50µL of buffer AE. A negative swab and reagent control, processed as indicated with sterile swab only or without the addition of blood, was included and did not result in PCR amplification.

All PCR reagents and set-up procedures were conducted in a separate room in a cabinet routinely pre-treated with ultraviolet light. PCR was performed using universal bacterial primers targeting the V2-V3 variable region of the 16S rRNA gene as outlined by Walter et al [31]. Briefly, the PCR mix consisted of the following: 2.5mM MgCl2, Amplitaq LD, 1xbuffer (all Applied Biosystems), 200µM dNTPs (Promega), 20pM of each of the following primers, HDA1 5’ ACTCTTACGGAG-GGCAGCAGT 3’, HDA2 5’ GTATTACCCGCGGCTGTCGAC 3’ and sterile water to give a total volume of 45µL. Template DNA (5 µL) was added and amplified under the following conditions: 94°C for 4 minutes; 30 cycles of 94°C for 30 seconds, 56°C for 30 seconds, 68°C for 1 minute and final extension step of 68°C for 7 minutes (Palm-Cycler CG1-96, Corbett Research). Positive (bacterial DNA only) and negative controls (PCR reagents and water only) were included in all PCR amplifications. PCR products were visualised by agarose gel electrophoresis.

The detection limit for the various sample types was determined by inoculating the swabs and blood samples with known amounts of Group B Streptococcus (102, 104, 106, and 108 CFU). Samples were subsequently frozen to mimic the collection
and storage procedures for the clinical samples, and then processed as outlined above. The detection limit for inoculated swabs and blood were 102 and 104 CFU, respectively.

The identity of the PCR products that were successfully amplified was determined via direct sequencing of the PCR product and by cloning and sequencing. PCR products were cloned into JM109 using the pGEM-T Vector System as recommended by the manufacturer (Promega). Individual white colonies were picked into 50μL sterile water, heated to 95°C for 10 minutes, allowed to cool to room temperature, and then 2.5μL was used as template in PCR reaction with SP6 and T7 primers utilising a PCR mix and similar protocol to that described for HDA primers above except an annealing temperature of 45°C was used. PCR products of the expected size from successful transformants were purified using the Wizard® SV Gel and PCR Clean-Up System as recommended by the manufacturer (Promega) and sent to the Australian Genome Research Facility for sequencing according to the sample submission protocol (http://www.agrf.org.au/). All sequence data was then analysed using the Chromas Pro Version 1.41 software (Technelysium, Tewantin, QLD, Australia). Where possible, double-stranded sequences were assembled. Sequences were analysed against the non-redundant nucleic acid database using BLAST[32] accessed through the NCBI database (http://blast.ncbi.nlm.nih.gov/).

Data
Statistical analyses were performed using the Predictive Analytics SoftWare (PASW) (PASW for windows. Release 18.0.2. SPSS: An IBM Company. Chicago Ill, USA, 2010). Categorical variables were assessed using Chi-square analysis and numerical values were assessed using non-parametric Mann-Whitney U tests with p values of < 0.05 considered significant.

Results
Forty-six neonates were enrolled into the study, 2 cases were control caesarean section deliveries at term. The median maternal age was 28.0 years (range 17-37; InterQuartile Range (IQR) 25-35.5), median gravidity was 2 (range 1-5; IQR 1-3) and parity 0 (range 0-3; IQR 0-1.5). The median gestation was 32 weeks (range 24-36 weeks; IQR 29.5-33) and median birthweight 1800 grams (range 720-2945 grams; IQR 1387-2135). Sixty one percent (27/44) were male infants and 57% (25/44) were singletons. Median Apgar scores at 1 and 5 minutes, respectively, were 7 and 9 (IQR 5.5-9.0; IQ 8-9).

Sixty one percent (27/44) were delivered vaginally with the median duration of rupture of membranes prior to delivery 3.0 hours (range 0-744; IQR 0-19). The median number of doses of antibiotics prior to delivery was 2 (range 0-143; IQR 1-14). Ninety three percent (40/44) received antibiotics prior to delivery and 67% (24/36) received a full course of antenatal steroids. Eleven percent (5/44) of women were noted to have a fever in labour, but in no delivery was the liquor described as offensive.

Bacteria were detected and identified by culture and 16S rRNA PCR/sequencing in 5 and 4 placental swabs, respectively, with bacteria detected by both methods in 1 sample (Table 1 and Fig. 1). Typical bacterial pathogens were identified by culture where-

Table 1. Identification of bacteria from culture and 16S rRNA PCR analysis from placental swabs.

<table>
<thead>
<tr>
<th>Patient*</th>
<th>Placental swab culture</th>
<th>16S rRNA PCR identification</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>Klebsiella pneumoniae</td>
<td>Negative</td>
</tr>
<tr>
<td>14</td>
<td>Negative</td>
<td>Lactobacillus sp</td>
</tr>
<tr>
<td>16</td>
<td>Skin flora</td>
<td>Negative</td>
</tr>
<tr>
<td>27</td>
<td>Group D Streptococcus</td>
<td>Negative</td>
</tr>
<tr>
<td>28*</td>
<td>Staphylococcus aureus</td>
<td>Streptococcus equinus</td>
</tr>
<tr>
<td>29</td>
<td>Negative</td>
<td>Mixed</td>
</tr>
<tr>
<td>36*</td>
<td>Group B Streptococcus</td>
<td>Negative</td>
</tr>
<tr>
<td>42*</td>
<td>Negative</td>
<td>Lactobacillus sp</td>
</tr>
</tbody>
</table>

* – patients for which placental inflammation was also evident (see Fig. 1)
as commensal vaginal flora was identified through 16S rRNA sequencing. Mixed flora was evident in separate swabs that were cultured and analysed by 16S rRNA (i.e. patients 16 and 29, respectively, Table 1). Bacteria were not detected by either method in any of the neonatal blood samples, nor in the two control samples obtained from term pregnancies.

Histological analysis revealed evidence of chorioamnionitis in 8 placentas (2 stage 1, 2 stage 2, and 4 stage 3), vasculitis in 4 and funisitis in 2 placentas (both stage 2). The relationship among culture, 16S rRNA, and placental histopathology was investigated (Fig. 1). Of all the placentas identified with inflammation (9 in total), bacteria were detected in 3 samples by 16S rRNA PCR and/or culture. Histological analysis of the placenta sample from patient 28 indicated the presence of both chorioamnionitis and vasculitis, a colony of S. aureus was cultured, and the 16S rRNA analysis revealed PCR products with high identity to Streptococcus equinus (Table 1). In general, however, there was no relationship between evidence of placental inflammation and the detection of bacteria (Table 2). Interestingly, bacteria were detected by culture or 16S rRNA in 5 samples where there was no evidence of placental inflammation.

To further investigate if detection of bacteria in placental swabs was related to inflammatory markers in the neonate, the FBC and CRP results were compared to detection of bacteria determined by the two different methods (Table 3). Exposure to a positive placental culture was associated with a statistically significant increase in band neutrophil ratio (p=0.04), but was not associated with any other significant difference in inflammatory markers including white cell count, neutrophil count, lymphocyte count and CRP.

**Discussion**

In our study 16S rRNA PCR analysis of DNA extracted from placental swabs did not increase the detection of bacteria potentially associated with preterm labour in comparison to routine placental culture. There were also no associations found with placental inflammation, neonatal inflammatory markers, positive cultures and positive 16S rRNA PCR.

The cause of preterm labour is multifactorial (11) with inflammation and infection being one causative factor. However, other studies that have used 16S rRNA PCR have reported a positive correlation with inflammatory markers and/or histology (20, 22, 26). Relative to these and other studies (33, 34), the incidence in our cohort of placental inflammation in general was low. This could be due to our wide range of gestations as the incidence of chorioamnionitis increases with decreasing gestation. The low incidence of inflammation and infection in our study is also likely to have been compounded by the very high administration rate of antibiotics. In our cohort, 93% of women received intravenous antibiotics prior to delivery which will reduce positive culture results. Gomez et al (35), however, reported that antibiotics do not completely eradicate intra-amniotic infection and thus a higher rate of positive 16S rRNA PCR results may be expected.

Sample type and methodology could also affect the ability to detect bacteria.

**Table 2. Statistical analysis of placental histopathology, positive placental cultures, and 16S rRNA PCR results.**

<table>
<thead>
<tr>
<th></th>
<th>Chorioamnionitis</th>
<th>Vasculitis</th>
<th>Funisitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=8</td>
<td></td>
<td>N=4</td>
<td>N=2</td>
</tr>
<tr>
<td>Positive placental culture</td>
<td>3/5 2/5 0.20</td>
<td>0/4 1/4 0.38</td>
<td>5/5 0/5 1.0</td>
</tr>
<tr>
<td>Positive rRNA PCR</td>
<td>2/4 2/4 0.13</td>
<td>3/4 1/4 0.31</td>
<td>4/4 0/4 1.0</td>
</tr>
</tbody>
</table>

**Table 3. Statistical analysis of neonatal blood, compared to placental culture and rRNA PCR results.**

<table>
<thead>
<tr>
<th>Neonate</th>
<th>Positive placental culture</th>
<th>Negative placental culture</th>
<th>p value</th>
<th>Positive rRNA PCR</th>
<th>Negative rRNA PCR</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median white cell count (IQ range)</td>
<td>13.2 (7-20)</td>
<td>12.4 (8.2-17.2)</td>
<td>0.67</td>
<td>12.1 (11.4-18.1)</td>
<td>12.4 (8.1-17.7)</td>
<td>0.64</td>
</tr>
<tr>
<td>Median neutrophil count (IQ range)</td>
<td>4.3 (2.9-4)</td>
<td>3.4 (2.2-5.7)</td>
<td>0.59</td>
<td>3.3 (3.3-9.9)</td>
<td>3.8 (2.2-6.2)</td>
<td>0.46</td>
</tr>
<tr>
<td>Median lymphocyte count (IQ range)</td>
<td>6.0 (3.7-7.9)</td>
<td>5.7 (4.2-8.1)</td>
<td>0.79</td>
<td>6.7 (5.7-7.9)</td>
<td>5.5 (3.9-8.1)</td>
<td>0.33</td>
</tr>
<tr>
<td>Median band neutrophil ratio (IQ range)</td>
<td>0.18 (0.05-0.45)</td>
<td>0.02 (0.01-0.12)</td>
<td>0.04</td>
<td>0.03 (0.01-0.05)</td>
<td>0.06 (0.0-0.13)</td>
<td>0.49</td>
</tr>
<tr>
<td>Median CRP (IQ range)</td>
<td>0.6 (0.05-72.4)</td>
<td>0.2 (0.2-1.0)</td>
<td>0.62</td>
<td>0.1 (0.1-1.0)</td>
<td>0.2 (0.2-1.0)</td>
<td>0.26</td>
</tr>
</tbody>
</table>
We chose to analyse placental swabs for bacterial DNA given that these are routinely collected for culture analysis, and are easily obtained with no risk to the patient. In contrast, other studies have extracted and analysed DNA from amniotic fluid (20-24), and fetal membranes and/or placental tissue (25-27). Similar to our results, discordance of PCR and culture results where (i) PCR and culture results are not the same (i.e. PCR positive culture negative, and vice versa), and (ii) the organism(s) identified by samples that are PCR and culture positive can be different, have previously been reported (20, 22-24). In contrast to our results, the number of positive 16S rRNA PCR results usually exceeded the positive culture results (20, 22-24), suggesting that there may be limitations in using swabs for this purpose. These limitations may include difficulty in obtaining a representative sample, sampling only the placental surface and not the underlying tissue, and difficulty in taking up and/or releasing the bacteria. The study by Jones et al (26) enforces the importance of sampling multiple sites of placenta to increase detection rates. They collected 5 different sections (central and peripheral) of the amnionic and chorionic placental membranes and found that the number of positive PCR samples varied from 1-5, with the number of positive samples/patient being highest for preterm and lowest for term births. Amniotic fluid may be advantageous over tissue and swabs in this regard as it represents a homogenous liquid sample that is relatively easy to process. The number of bacteria taken up and released by swabs can be influenced by swabbing technique during collection of the sample, swab material, and wetting solutions (36). Utilisation of flocked nylon swabs may improve collection and recovery of bacteria (36, 37).

In one sample, the placental histology, culture and PCR results corresponded, with S. aureus cultured, and sequences highly homologous to S. equinus obtained from the 16S rRNA analysis. As noted previously, other studies have observed differences between culture and PCR results, which in this case may be due to factors such as higher numbers of S. equinus than S. aureus in the sample and/or problems in culturing S. equinus under the standard conditions utilised. As the name suggests, S. equinus was originally isolated from horses, and has been isolated from human, animals and food products (38). This organism has occasionally been implicated in human infections in patients with other comorbidities (39-41). There are no reports in the literature on the involvement of this organism in preterm birth.

Conclusions
In our population with a low rate of positive placental culture results, 16S rRNA analysis of placental swabs does not significantly increase the detection of bacteria potentially associated with preterm delivery. Placental swabs may not be the best samples to use as other studies have successfully detected diverse taxa from amniotic fluid and placenta using a similar DNA based approach. The challenge will be to develop a non invasive, highly sensitive assay to further investigate the role of bacteria in preterm birth.

Acknowledgements: We would like to thank RN Margaret Broom for assistance with recruitment of infants into the study. We would also like to thank Dr Janice Abbey, Chris Munday and David Stephenson for assistance with development of the PCR technique.

References:


ART MED

A Surprising Synergy

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Health care professionals are visiting art galleries in increasing numbers to participate in programs that link art and medicine in new and stimulating ways. Works of art can inspire and perplex viewers and when time is spent absorbing visual material in the gallery environment unexpected interpretative challenges arise. When a topic is included to focus discussion, students and practitioners can begin to think broadly and conceptually about issues with significant relevance to their working environment.

So….what do art and medicine have in common? The intersection of art and medicine begins with the fact that in most cases both disciplines focus on objects. In an art gallery or museum we treasure our collections keeping them in an optimal environment where the temperature and humidity are controlled, exposure to light is minimised and specialist conservators carefully monitor conditions. Each work of art has an embedded history which is referenced in the way it is displayed and interpreted for the visiting public. Similarly, in medicine, the patient is the focus with their own personal history, cultural background, genetic profile etc. Healthcare providers also work diligently to keep their patients functioning at an optimum level. With both disciplines, however, the ultimate challenge lies in the unseen - that which is not so readily revealed and requires considered contemplation and time to discover.

artmed is a collaborative program between the National Gallery of Australia (NGA) and the Australian National University Medical School (ANUMS). The program involves first year medical students visiting the Gallery in small groups to view works of art that relate to topics in the ethics, law and human rights area of the curriculum. Prior to the group’s visit Gallery education staff familiarise themselves with topic readings and choose three works of art that will promote a vibrant discussion during the 90 minute session.

Topics that have been discussed in recent artmed sessions include euthanasia, the Northern Territory intervention, doctor health and well-being, informed consent, mental health and clinical competence. During the session students are initially encouraged to develop their observational skills by looking closely at the work of art using some of the key elements of visual analysis as a framework. These include colour, texture, line and shape. There is usually much discussion during this process as members of the group convey their response to the work of art whether it is a painting, sculpture, print, photograph, installation, performance piece, multimedia or ephemeral work.

Students are frequently surprised by the diversity of responses in this part of the session and on many occasions they are confronted by the realisation that they overlook certain elements that others notice. All areas of the Gallery’s collection are utilised including the well-known paintings of Claude Monet and Jackson Pollock, the inspiring Aboriginal and Torres Strait Islander collection, Asian art, Ballets Russes costumes and contemporary photography.

Once the students have honed their observation skills and talked about what they see, the session continues with interpretative analysis and then links are made between the work of art and the topic area. The painting on the cover of this issue of the MSJA, Daphne and windpump 1973 by Arthur Boyd, was painted not long after the artist returned to England after undertaking a Creative Arts Fellowship at the ANU. It has been used as a stimulus for the topics of informed consent and doctor health and well-being.

Offering a variety of interpretations students have spoken about the vulnerability of the smaller figure who appears to cower before the larger and more threatening form entering the scene from the right. Conversely, is this individual reaching out with a symbolic offering of three upturned paintbrushes? The fractured windmill appears as a dysfunctional object in the desolate landscape overseen by a magical azure sky. What occurred before and after this snapshot of an iconic rural scene set in the vastness of regional Australia - a place made more overwhelming by Boyd’s decision to fill much of the painting with land tipping over the horizon line to reveal more of the same.

As the mysteries of the work of art are discussed, the gallery setting encourages students to relax and challenge themselves to establish the meaning of complex works of art. Some students find this shift in their thinking to be a confronting exercise. The gallery space is a place of ideas, works of art resist a definitive conclusion and organic discussions provide a vibrant training ground for some of the more difficult issues faced in contemporary medical practice. By listening to one another and respecting the value of individual responses, subtle changes occur in the group dynamics during the session.

The artmed program is now an integral component of the first year medicine curriculum, and even though not compulsory, most students will choose to visit the Gallery as part of this unit of study. On return to university they present to their cohort using images from the Gallery’s collection as a stimulus for wider group discussion. By the completion of first year, in addition to their on-site visit, medical students will have participated in up to twelve sessions at university during which works of art from the National Gallery’s collection have been projected and discussed in the lecture theatre. However, nothing can replace the powerful experience of sitting for a lengthy period in front of a work of art in the gallery setting and allowing ideas to flow.
The artmed program now offers further opportunities for medical students to engage more deeply with the National Gallery’s collection by applying for a research position based at the Gallery for a twelve-month period. During this time successful students have access to the institution’s vast collection of over 160,000 works of art, the Research Library, Collection Study Room as well as the opportunity to meet with art gallery professionals.

The inaugural research project, *The depiction of sexuality and sexual well-being in Aboriginal and Torres Strait Islander art* has now been completed and it is hoped the student involved will deliver a lunchtime talk at the Gallery in the near future. Topics for this year’s projects are *Representations of death in modern art*, *A Neurological study of the Frances Derham collection of children’s art* and *Transgenerational Trauma in Contemporary Art.*

Another opportunity now also exists with the recent completion of an extended artmed program consisting of four consecutive visits for a group of ten students. A highlight of this initiative was the students’ presentations in the final week where each spoke about an inspirational work of art in the Gallery’s collection.

The artmed collaboration has also stimulated interest from staff at The Canberra Hospital with groups of Clinical Directors, Medical Directors and Nursing Unit Managers participating in sessions over the last eighteen months.

The artmed program provides medical students with a rare opportunity for individual and group reflection during their busy academic year. The unique gallery setting can unlock inhibitions, promoting dialogue relevant to the practice rather than the mechanics of medicine. As Kahlil Gibran suggests, reason has its limitations when practised in isolation. Looking at art, thinking about art and talking about art, especially when made relevant to the healthcare environment, can help make medical students more astute, considered and reflective doctors. The visit demystifies the Gallery and affirms the potential for art to intersect with the medical world.

**Addendum:**
*Frances Wild gained her general nursing qualification at St Vincent’s Hospital Sydney in 1982 and was a Registered Nurse until 1990.

The artmed program appears in the National Gallery of Australia’s 2013-2016 business plan - an indication of the Gallery’s continuing commitment.

**Acknowledgements:**
My thanks to Professor Tom Faunce, Dr Christine Phillips and Ruth Townsend at ANU for their support of the artmed program. Thanks also to my colleagues at the National Gallery of Australia, Margie Kevin and Ingrid Anderson who provide invaluable assistance with the artmed program.
Amie McCosker, 2014, Drawing.
Caption: “You can still smile even if one facial nerve gives up”
Physiotherapy experiences in Vietnam

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I
n December 2012, I was given the opportunity to work in a hospital in Vietnam through a scholarship awarded by the Hoc Mai Foundation which is a partnership program established with the University of Sydney and its Vietnam counterparts. Whilst working in the Vietnamese healthcare system, my primary aim was to learn more about specific healthcare delivery in Vietnam, especially the patient/therapist relationship as well as the modality of treatments most commonly used within the context of physiotherapy. My preconceived idea of this relationship, or ‘therapeutic alliance’, which has been shaped by my experiences in the Australian healthcare system, is that health care is patient centred and any clinical decisions made are relevant and are with the best interests of the patient in mind. As a result, ideally the therapist needs to possess traits such as an ability to empathise and also have good communication skills. With respect to treatment, I was keen to observe if there was more of an emphasis on medicine, an approach more towards staying active with exercise or a mixture of both. Of course growing up in Australia with a different cultural and social background naturally meant that I was expecting a major disparity in terms of physiotherapy assessment and treatment in Vietnam.

I was allocated to work at the largest hospital in Vietnam, Benh Vien Bach Mai Hospital situated in Vietnam’s bustling capital city, Hanoi. I spent my month in the hospital’s Spinal Cord Rehabilitation Unit. As a 3rd year physiotherapy student at the time, I had just completed my rehab placement in Sydney. Under the supervision of a Senior Physiotherapist, I was exposed to patients with a variety of different spinal cord related problems from complete cervical fractures to disc herniations. Unfortunately, due to the main mode of transport in Vietnam being motorbikes, many of the patients who arrived at the Spinal Cord Rehab Unit had motorbike accidents as their mechanism of injury. As a result of limited resources and equipment in the Spinal Cord rehab unit, (such as arm ergometers, stationary bikes and a harness system on the treadmill among others) the physiotherapists mainly relied on passive techniques to treat patients which included static stretches and massage as well as forms of electro-physical agents such as interferential and therapeutic ultrasound. Whereas in Australia the patient’s active involvement with treatment is strongly encouraged with respect to not only spinal cord injuries but to impairments in general, in Vietnam the patient essentially has minimal input with regards to the form of treatment they are receiving. This confirmed by preconceived notion that due to the influence of culture and social attitudes, in Vietnam the therapist is the main driver behind which treatments are provided to the patient.

What I admired most of all during my one month placement was how family oriented healthcare is in Vietnam. During my time at the rehab unit, the family members would literally carry the patients in and then transfer them from the wheelchair to the bed. Imagine if this occurred in Australia!

Consequently he was unable to walk and was wheelchair bound. How would you feel if this happened to you at this age? Frustrated? Angry? Indeed it was understandable for the patient to harbour these thoughts. However, despite these sentiments and his poor prognosis, he worked unbelievably hard in an attempt to restore some function. For me, this epitomised the willingness and courage of the patients I had seen in the Spinal Cord Injury Unit to improve their physical condition and quality of life.

I am extremely grateful for the opportunity to work in the Spinal Cord Rehabilitation Unit at Benh Vien Bach Mai hospital. The experience has altered my perception regarding assessment and treatment techniques which I’m sure I will utilise back home in my practice. Vietnam is an amazing country and I whole-heartedly recommend either as a physiotherapy student or a practising physiotherapist, to spend some time working in one of Vietnam’s hospitals as it will provide some invaluable experience and enrich one’s personal development in the field.
Ethical and Legal Issues in Refugee Child Health

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Introduction

Children comprise approximately 40-50% of the refugees who are accepted to Australia each year under the Humanitarian Program. At the same time, a significant number of additional children enter Australia seeking refugee status, either as asylum seekers or through the Family Reunion Program (1). As a result of adverse socio-political circumstances, these children/adolescents are likely to have suffered significant traumatic events, losses, separations or threats before and/or after arrival in Australia, placing them at increased risk of poor health outcomes. Particular health needs that warrant special attention in this population are nutritional deficiencies, growth and development, immunisation and infectious diseases, mental health and dental health (2).

Case Report

AB is a 14-year-old asylum-seeking child from the Middle East who has been in Australia with his biological father for less than 12 months, 4 months of which he spent in an Australian detention centre. Before his arrival in Australia by boat, AB and his father spent one month in an overcrowded camp in Indonesia. They are now in community detention and live in an apartment provided by the government. The remainder of AB’s immediate family, including his mother and siblings, are also asylum seekers and are currently confined to a detention centre elsewhere in Australia.

AB attends an Intensive English High School in a major metropolitan city and enjoys playing soccer. He was reviewed by the Community Refugee Health Service because of a positive Quantiferon Gold result (indicating he required a further assessment for tuberculosis), which was picked up through a newly embarked upon health screening program at the school. AB and his father reported no significant presenting or past medical history. AB currently takes daily antibiotics for his acne, and reported no known allergies.

AB reported he did not have good social support, having no close person to confide in. AB reported often missing his mother and feeling sad. AB admitted to having experienced low mood, but denied suicidal ideation. There was no evidence of domestic violence or neglect at home. AB denied any history of smoking or use of alcohol or recreational drugs.

Discussion

Ethical and Legal issues in refugee health:

Refugees who enter Australia under the Humanitarian Program are recognised to have the same right to health care as citizens of the resettlement country, in accordance with the 1951 United National Convention relating to the Status of Refugees, of which Australia is a signatory (1). The Convention not only states ‘provision of necessary medical assistance and health care to all children,’ but also supports facilitation of protection, provision and participation in society (2).

Equity

Refugees often arrive with pre-existing health conditions, exacerbated by socio-cultural factors such as language barriers, trauma, financial constraints and resettlement difficulties.3 Subsequently, health professionals may be called upon to provide health care for these children and their families. In those circumstances, health providers are expected to uphold justice in health care, which denotes ‘fairness or equity of responses to health needs,’ irrespective of race, religion, sex, occupation, social standing or ability to pay (4). This entails not only curative aspects of care after an accurate diagnosis, but also an emphasis on preventive medicine.

Gaps in delivery of equitable health care however exist, and this is partly attributable to the current legislation and policies as exemplified by the fact that approximately one third of asylum seekers in the community are ineligible for Medicare (2). The major contributing factors to the health inequities are visa categories, location of placement and/or refugee status (2, 3, 5).

AB’s right to equity was challenged by a number of hurdles. AB and his father remain asylum seekers in ‘community detention’ and are thus ineligible for Medicare. Access to healthcare was facilitated by a non-government organisation, helping to overcome financial barriers in accessing GP and the Child Refugee Service. However, notable systemic deficiencies are evident as the finding of suspected tuberculosis was incidental and only found because
AB attended a particular school. AB’s access to health care for this issue was therefore delayed.

It is often assumed that refugees migrating under the Humanitarian Program undertake comprehensive pre-departure and post-arrival health screening, but this is only partly true. The Australian Government mandates health assessment before a visa is issued, which consists of a general medical examination, growth measurement and urinalysis if over 5 years of age. However, Australian States and Territories have varying policies and coverage for post-arrival checks. In addition, the quality of pre-departure medical screening, if conducted, may vary considerably, depending on the country of origin (1, 6).

Because AB arrived in Australia as an asylum seeker, no pre-departure screening was conducted. After his arrival, he underwent a post-arrival health screening similar to other adult migrants seeking refugee status in Australia, which included basic physical examination, blood tests, and infectious disease screening all reported to be “normal”. AB has not had any contact with health providers since then, largely attributed to socio-cultural barriers to accessing health care as well as preoccupation with basic survival in a new country.

The principle of social justice for AB would have been easily jeopardized if he was attending a school at which the health screening program was not in place. This illustrates that there exists a clear gap in equal distribution of resources not only between the refugee and host populations but also within refugee/asylum-seeker populations. It is also well established that children in detention have additional difficulty accessing health care, which would have been the case for AB when he was in detention himself (1, 2).

Therefore, improved awareness amongst health professionals of current laws and policies concerning variation in access to health care in refugee populations is warranted, so as to ensure effective advocacy for distribution of resources and appropriate referral to available services (2, 5).

**Patient Autonomy and Confidentiality**

Western medical ethics have evolved on the foundation of patient autonomy and beneficence, a cornerstone of which is informed consent. Informed consent requires that a person must be able to make an autonomous choice between options, according to the individual’s own values. Therefore, it can be accomplished only when provision of adequate information and patient’s ability to critically evaluate attendant benefits and risks for a rational decision are both present. It is not merely a patient’s right but is, indeed, central to the safety and quality of patient care (7, 8).

Barriers to patient autonomy in refugee families can be described as ‘triple threats’: a) language barrier, b) cultural differences, and c) low health literacy. These barriers impair effective bi-directional communication between health provider and recipient (9). In such circumstances, interpreters are frequently called upon to bridge that gap, and they may also act as culturally appropriate advocates for the client.

Family members, especially children, are often used in practice to bridge the gap by providing interpreting services. However, this is problematic as not only do children often have inadequate health literacy, it also distorts the child-parent relationship and places a substantial emotional strain on the child (2, 9, 10).

Cultural barriers exist because perception about illness and its causality, gender roles, and customs and practices may vary significantly by culture. Although practitioners need not agree with the patient’s culture-bound beliefs, cultural sensitivity and competency will enhance understanding of the refugee families and enable the provision of optimal holistic care for individual patients. Importantly, it is crucial to be aware of socio-cultural stigma and shame associated with sensitive health issues, such as sexual abuse, domestic violence, substance abuse or mental health problems, especially in small communities (2).
In addition to this triple threat, refugee families may mistrust authority figures as a result of previous traumatic experiences (e.g. detention, camps) and a fear that recognition of certain health problems may act against their application for residency status or the capacity for family reunion (2). Acknowledgment of these variables is essential as they can act as coercive influences, further jeopardising autonomy, mutual trust, attendance, and compliance (6).

In consultation with AB and his father, the above-mentioned variables were acknowledged through assistance from an over-the-phone interpreter who aided in establishing rapport by bridging the gaps in language and culture, facilitating AB’s autonomy. It was however difficult to obtain AB’s detailed past medical history. When AB and his father were interviewed separately, additional history emerged that the family had previously fled to another country with new identities when AB was young. In this context of stress and dislocation it might be understandable if routine medical history could not be accurately recalled, perhaps compounded by low health literacy.

After excluding active signs and symptoms of active TB, AB was then referred to a Tuberculosis Specialty Clinic, where he will receive appropriate investigations and management if required. Since AB is now linked with suitable health providers who are capable of coordinating appropriate health services in a culturally sensitive manner, it seems promising that his rights in terms of justice will be better met in the future. Nonetheless, the systemic failure to support and integrate refugee health services within the national public health will always result in generating ‘unlucky’ refugee children who are lost in the systemic gaps and who, despite their rights, receive suboptimal health care.

**Conclusion**

Refugee children are amongst the most vulnerable groups in the society, not only because they are at a stage where their bio-psycho-social development is being largely influenced by environmental factors, but they also face physical and psychological trauma, social isolation, and deprived exposure to developmentally appropriate stimulation. Being unaccompanied or separated from family members can create further strain on the children.

The dynamics of socioeconomic factors combined with the many other barriers to health care create challenging conditions for clinicians who try to uphold the principles of equity and justice for this population.

The situation warrants a greater need for health professionals to take on an advocacy role to effect system-wide change, supported by strong evidence that with early and appropriate support and intervention refugee children, who often possess incredible resilience, can achieve their fullest potential (2).

**Author’s Note:** Details including names, institutions and specific dates have been changed to protect the anonymity of the child.

**Acknowledgements:** nil

**Conflicts of interest:** none to declare

**Stock image:** Refugee Child, William H. Johnson

WikiMedia Commons

**References:**

Bullying is increasingly being recognised by communities and governments as detrimental to the development and well-being of children. It is a complex sociocultural phenomenon affected by many aspects of a child's interaction with their community. Intervention programs aimed at reducing bullying are more likely to succeed if they do not just treat the bully or victim in isolation, but also consider the extended social environment. Therefore, as an important part of the community, the general practice may be able to play a role in reducing bullying and preventing subsequent harm. This view is supported by The Royal Australian College of General Practitioners and the Australian Medical Association.

Definition and Scope of Bullying

Bullying is unjustified aggressive and oppressive behaviour where dominant individuals (bullies) intentionally cause mental or physical harm to others (victims). While this behaviour is regarded as intentional, it may be the result of a socio-cultural phenomenon where social groups are formed with different levels of power. This involves a complex set of social processes of which children are largely unaware (1). It arises from an imbalance of power that favours the bullies, with the power imbalance increasing as the bullying continues (2). Traditionally, there was a belief in the community that bullying was limited to physical abuse but there is now awareness that bullying includes verbal as well as indirect forms (such as using slander, spreading rumours, excluding others from activities and the use of manipulation) (3). More recently it has expanded to include cyber-bullying (the use of information and communications technology) (4-7), the results of which have generated high profile case-reports in the media (see reference 8 for an example of such a report) (9).

Prevalence

The prevalence of bullying varies greatly between studies, from around 10 to 50 percent (10-15). This is largely due to the evolving means by which bullying is conducted, as well as society's attitudes and understanding of bullying (11, 16). For example, varying styles of bullying between the genders may account for the difference in measured prevalence between boys and girls (see Table 1). In a recent study of 20,832 Australian children aged 9 to 14 years, one in four reported being bullied every few weeks and one in ten reported bullying others every few weeks (17).

Risk Factors

Factors that predispose a child to being a bully, or being targeted by a bully are listed in Table 1. They are a combination of physical, behavioural, environmental and personality factors. In brief, male victims are generally younger and physically weaker than their peers, while bullies are more likely to be physically stronger (11, 18). Interestingly, other physical deviations from the norm (such as being overweight, wearing glasses or speaking with an uncommon dialect) may not play as great a role (11). Victims are more likely to be sensitive, quiet and insecure than bullies (11, 19, 20), who are often not only aggressive to their victims, but also to other peers and adults. The victim's response to being bullied is often to withdraw, with younger children sometimes crying. Bullies may be rewarded for their behaviour with money or food from their victims and respect from their peers (11). A child's home environment plays an important role, with children more likely to be bullies if their parents provide little emotional support and interest, or if they use physical punishment (21, 22). Lack of supervision, not setting rules and tolerance of bullying behaviour is also associated with increased bullying behaviour (11, 17, 23, 24). Cyber-bullying is therefore a potentially large issue as adults may be unfamiliar with it and hence less able to supervise its use (25-27).

Adverse Effects

It is recognised, both in Australia and overseas, that bullying during childhood and adolescence is harmful to the development of both victims and bullies (28-30). In victims it has a direct negative impact on academic performance (14, 31-37) and increases the risk of developing psychiatric illness and associated symptoms during childhood (11, 16, 38-46) and adulthood (24). Bullies are also more likely to have poorer academic performance compared to their peers (14, 35-37) and are at increased risk of being violent and being involved in criminal behaviour as adults (11, 47).
Typical victim | Typical bully
--- | ---
**Child’s physical attributes** | Younger and physically weaker males are more likely to be victims (11, 15). More boys than girls are victims (11, 15, 17). | Male bullies are more likely to be physically stronger (18). More boys than girls are bullies (11). |
**Child’s personality** | Generally cautious, sensitive, quiet, anxious, insecure and have low self-esteem (11, 19, 20). Often do not have any friends (11, 14). | Less anxious and insecure than peers (11, 19, 20). Aggressive to peers and often aggressive to adults with a need to dominate others (11). Often impulsive (11). |
**Child’s view towards violence** | Negative view towards violence (11). | More positive attitude towards violence and use of violent means and have little empathy with victims (11). |
**Child’s immediate response to bullying** | Withdrawal. Younger children may cry (11). | May be rewarded with money, food or respect (11, 17). |
**Mental, physical and social manifestations** | Depression, anxiety, difficulty sleeping, phobia of school, low self-esteem, loneliness, feelings of unattractiveness, shame, social marginalisation, isolation and somatic symptoms (such as bed wetting, abdominal pain and headaches) (11, 16, 38-46, 48, 74-76). | Satisfaction and possibly improved social status (11, 17, 74). Increased rates of smoking and drinking (14). |
**Suicidal ideations** | Increased thoughts of suicide in both sexes, more so in females (77). | Increased thoughts of suicide (77). |
**Effect on academic performance** | May have reduced academic performance and increased school absenteeism (1, 14, 31-37). | Poor academic performance (14, 35-37), but may not be a causal factor (78). |
**Contributing factors from adults** | More likely to be depressed and insecure in adulthood (24, 79-81). Less likely to be involved in crime as an adult (11). | More likely to have antisocial behaviour, increased substance and alcohol abuse, violence and legal problems as an adult (1, 11, 14, 45, 47, 82-85). |
**Contributing factors from adults and society** | Parents/carers and teachers’ attitudes, tolerance and rules around bullying affect the extent of bullying (11, 23, 24, 86). Family socioeconomic status is not a risk factor for being a victim or bully in most Northern American and European countries (15). More likely in Australian Government schools (17). | Negative emotional attitude by the parents and carers (e.g. lack of warmth or involvement) or use of physical punishment (21, 53, 87-89). Lack of supervision and interest by parents and carers in activities outside of school (22, 88, 90, 91). |
**Other types of victims and bullies** | Provocative victims: Have anxious and aggressive reaction patterns, and problems concentrating. This behaviour irritates others and results in negative reactions. These victims may also be labelled hyperactive (11). | Passive bullies: Participate but do not usually initiate bullying behaviour. These individuals have mixed personalities (11). |
| Bystanders: | Perceive victims as physically or psychologically weaker, and admire bullies (92, 93). Empathy for victims wanes with age (93). |
Intervention Programs and Studies

The first major study to show that bullying could be reduced was conducted between 1983 and 1985 in Norway (48). Since then, a number of programs have been implemented around the world in an attempt to reduce bullying. The Australian government recognised the importance of bullying when the House of Representatives published the Sticks and Stones report in 1994 (49). Subsequently, each state and territory in Australia has developed policies and guidelines to address bullying in children (see Appendix 1 in reference 2 for a brief review). However programs developed as a result of these policies are often not based on evidence (50, 51), vary greatly in their approach and are not effectively evaluated (2, 3, 52). Not surprisingly, reviews of these programs have shown mixed results (2, 3, 53-58). Despite this, some themes on effective strategies in reducing bullying have emerged:

1. Whole-school interventions are more effective than programs that are more limited (56, 58), possibly reflecting the fact that bullying is a complex multi-factorial social phenomena involving bullies, victims, peers, adults, parents, school environments and home environments (57). A recent meta-analysis gave support to this, finding a 20 percent reduction in the rates of bullying and being bullied where whole-school programs were implemented (59).
2. Programs are more likely to succeed if schools have a degree of autonomy and are not controlled by external organisations (2).
3. Programs may be more effective if they target younger children (2, 3, 60) and girls (2).
4. Programs need to be sustained as the rates of bullying behaviour return to baseline levels after programs end (2).
5. Programs that target bullies with behavioural solutions may be less likely to be successful than those that focus on helping the victim. This may be because victims have a stronger immediate incentive to change and are less likely to have contributing negative factors at home (3, 60-62).

Policies in ACT Schools

The policies concerning bullying in ACT public schools are
Table 2. Prevention strategies of the general practice to reduce bullying in the community.

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<tr>
<th>Strategy and justification</th>
<th>Level of prevention (94)</th>
<th>Responsibility</th>
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<tbody>
<tr>
<td>Encourage cultural change and changes in societal attitudes</td>
<td>Primordial</td>
<td>All</td>
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<tr>
<td>Many of the strategies that are aimed at reducing bullying behaviour at the primordial level may be small and largely philosophical, but are easily implemented and will foster a world-view that will improve the success of strategies aimed at other levels.</td>
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<tr>
<td>1. Make everyone welcome and bulk-bill those in need.</td>
<td>Primordial</td>
<td>All</td>
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<tr>
<td>2. Promote transparency by not accepting gifts from drug companies (95) or patients.</td>
<td>Primordial</td>
<td>All</td>
</tr>
<tr>
<td>Encourage research into bullying and funding for anti-bullying programs</td>
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<td>3. Practice and thereby promote evidence-based decisions.</td>
<td>Primordial</td>
<td>Doctors</td>
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<tr>
<td>4. Order tests and drugs wisely, saving the community money.</td>
<td>Primordial</td>
<td>Doctors</td>
</tr>
<tr>
<td>5. Join the AMA to support their anti-bullying campaigns and evidence-based practices.</td>
<td>Primordial</td>
<td>Doctors</td>
</tr>
<tr>
<td>6. Write to politicians and influential members of society who are involved in anti-bullying campaigns, awareness and research. Stress the importance of using evidence-based methods and evaluation.</td>
<td>Primordial</td>
<td>Manager</td>
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<tr>
<td>Promote community awareness</td>
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<tr>
<td>7. Have posters and pamphlets in the waiting room that promote social behaviour encouraging loving home environments (see Table 1). For example, posters on domestic abuse, discrimination and happy well-connected families.</td>
<td>Primordial, Primary</td>
<td>Secretary</td>
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<tr>
<td>8. Have the AMA pamphlet on bullying directed to children, “Bullying: What you need to know,” (70) available in the waiting room.</td>
<td>Primary-Tertiary</td>
<td>Secretary</td>
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<tr>
<td>9. Have posters (see reference 96 for an example) in the waiting room that encourage people to act if they experience or witness bullying (97).</td>
<td>Primary-Tertiary</td>
<td>Secretary</td>
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<tr>
<td>Involve local schools.</td>
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<td>10. Encourage local schools to use evidence-based methods and become involved in multi-school studies, such as those conducted by the Child Health Promotion Research Centre (67).</td>
<td>Primordial-Quaternary</td>
<td>Manager</td>
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<tr>
<td>11. Offer to give a talk to the children of the local schools, and convey the following information:</td>
<td>Primary-Tertiary</td>
<td>Manager, Doctor or Nurse</td>
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<tr>
<td>i. Society’s negative view on bullying.</td>
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<td>ii. Scope of bullying and its effect on individuals.</td>
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<tr>
<td>iii. Children are not alone and adults are there to help.</td>
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<td>iv. Children can talk to any adult they feel comfortable with or with the staff identified in strategy number 12.</td>
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<tr>
<td>v. Encourage children to develop a sense of responsibility towards preventing bullying behaviour by reporting it to an adult (97).</td>
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<tr>
<td>vi. Provide age-appropriate resources they can access about bullying (for example those listed in reference 70).</td>
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<tr>
<td>vii. Reassure children that if they are still worried they are welcome to visit the general practice.</td>
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<td>viii. Give details of where the practice is located, how to get to it on public transport, confidentiality, and that there is no cost to them.</td>
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<tr>
<td>ix. Have this information available in pamphlets at the school.</td>
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<tr>
<td>Strategy and justification</td>
<td>Level of prevention (94)</td>
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<td>12. Identify contacts at the local schools, such as the principals, school network leaders, school</td>
<td>Secondary, Tertiary</td>
<td>Manager</td>
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<tr>
<td>councillors, and school psychologists. Also identify other people and organisations in the</td>
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<tr>
<td>community, such as community workers, community psychologists and psychiatrists and child</td>
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<td>protective services. Make this information available to the staff.</td>
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<td>13. Ask for information on the school’s programs and procedures for dealing with bullying and</td>
<td>Secondary, Tertiary</td>
<td>Manager</td>
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<tr>
<td>if it is a major problem for the school. Use this information to get a sense of which schools are</td>
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<td>better equipped at dealing with bullying.</td>
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<tr>
<td>14. Provide the AMA pamphlet on bullying directed to children “Bullying: What you need to know”</td>
<td>Secondary, Tertiary</td>
<td>Manager</td>
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<tr>
<td>(70) to the local schools. On the back, put the practice’s contact details, opening hours,</td>
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<td>information on how to get to the practice using public transport, emphasising there is no charge</td>
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<td>or need for a Medicare card and that in most cases confidentiality will be kept for children 14</td>
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<td>years and older.</td>
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<td>15. Encourage local schools to keep good statistics, modify their programs if appropriate, and</td>
<td>Quaternary</td>
<td>Manager</td>
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<td>publish any positive or negative findings.</td>
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Make children feel comfortable

It is important to make children feel comfortable when talking about their issues to a doctor as their preconceived view is that doctors cannot deal with their issues (98).

| 16. Identify which doctors are particularly good at and/or enjoy communicating with children.     | Primary-Tertiary         | Manager        |
| 17. Ask the child if he/she has any preference on what type of doctor they want to see (for       | Primary-Tertiary         | Secretary      |
| example, male or female) and refer him/her as appropriate.                                      |                          |                |
| 18. Reassure children that what is discussed is, with a few exceptions, confidential.            | Secondary, Tertiary      | Doctors        |
| Tertiary                                                                                        |                          |                |
| 19. Encourage children to return to the practice if they feel unhappy.                           | Secondary                | All            |
| 20. Give the child and/or family the AMA pamphlet (70) with information on bullying and other     | Secondary, Tertiary      | All            |
| resources they can access.                                                                      |                          |                |
| 21. When dealing with children, talk at an appropriate level and use phrases as suggested in the   | Secondary, Tertiary      | Doctors        |
| AMA pamphlet (69). Be aware that children may present for a reason other than bullying because they are embarrassed, or they present with symptoms caused by bullying (for example, depression and anxiety). |                          |                |
| 22. Encourage children to befriend anyone they know who may be bullied and to encourage them to | Tertiary                 | All            |
| talk to the school, or visit the practice if they feel unhappy.                                 |                          |                |
| 23. Make the practice child friendly by having age appropriate toys and books.                   | Tertiary                 | Secretary      |
| Involve the family and school.                                                                  |                          |                |
| 24. Try to consult with the family and encourage them to raise the issue with the school           | Secondary, Tertiary      | Doctors        |
| personnel identified in strategy number 12, as every school is required to have a strategy for    |                          |                |
| dealing with these issues. However, acknowledge that the school’s resources are limited and if   |                          |                |
| the child or family are not satisfied with the school’s response, offer to write a letter or      |                          |                |
| make a phone call to the school (69).                                                          |                          |                |
| 25. If cyber-bullying may be an issue, encourage parents to monitor and restrict child’s phone     | Secondary, Tertiary      | Doctors        |
| and internet usage.                                                                           |                          |                |
### Strategy and justification

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<td>26.</td>
<td>Mention that it may help to change school environments and mention schools which you believe (from strategy number 12) may be better equipped at dealing with these issues. In particular there may be less chance of bullying at a non-government school (17).</td>
<td>Tertiary</td>
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#### Screening.

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<td>27.</td>
<td>For any woman who is pregnant, but particularly for those who are not in a position to provide a family environment that is supportive of a child, counsel her and her partner on their rights and your support in her/their decision in terms of family planning.</td>
<td>Primordial</td>
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<td>28.</td>
<td>Treat and/or refer parents and parents-to-be with mental health or other issues that may be impacting on the quality of family life.</td>
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<td>29.</td>
<td>Opportunistically identify children at risk and consider referring them for counselling or treatment (for example, children with behavioural issues such as inattention may be victimised (72), yet can be treated).</td>
<td>Primary</td>
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<td>30.</td>
<td>Identify children who are in an abusive family environment and attempt to refer the family for counselling or report them to the authorities (if appropriate, for example, if physical abuse is suspected). Educate parents and carers of the consequences of their behaviour on their children, in particular the benefits of a loving, non-hostile family environment (11).</td>
<td>Primary, Secondary</td>
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<td>31.</td>
<td>Have parents of children complete a screening form for potential behavioural and development issues (such as the Parent Evaluation of Developmental Status (PEDS)) (65).</td>
<td>Primary-Tertiary</td>
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<tr>
<td>32.</td>
<td>Have children over 12 years old complete a questionnaire to screen for mental health issues (such as depression and anxiety) while in the waiting room (65).</td>
<td>Primary-Tertiary</td>
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<td>33.</td>
<td>Make staff aware of the personality types, behaviours and environments (refer to Table 1) that predispose children to being bullied or bullying. Emphasise that bullies as well as victims are likely to benefit from discussions (69).</td>
<td>Primary-Tertiary</td>
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<td>34.</td>
<td>Have staff red-flag children or families they believe should be further screened for bullying by doctors.</td>
<td>Primary-Tertiary</td>
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<td>35.</td>
<td>Ask children about academic performance, friends, smoking, ideas about self-harm and relationships with adults (in particular parents).</td>
<td>Secondary, Tertiary</td>
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<tr>
<td>36.</td>
<td>At any stage, consider referring a child and/or family to a psychologist, youth worker or social worker (69).</td>
<td>Tertiary</td>
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#### Evaluation

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<td>37.</td>
<td>Ask schools if they can collect metrics on the use and perceived role of the general practice by the students and parents in the statistics they collect (63, 64). Use this information to modify these strategies.</td>
<td>Quaternary</td>
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<td>38.</td>
<td>Discuss the effectiveness of this program regularly, and use the educated opinions of staff, feedback from parents and children, feedback from the local schools, and the presentations of individual case studies to evaluate the effectiveness of this program. Modify these strategies as appropriate.</td>
<td>Quaternary</td>
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<tr>
<td>39.</td>
<td>Keep up to date with the latest research and modify these strategies as appropriate.</td>
<td>Quaternary</td>
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consistent with the broad findings above. Furthermore, they are not prescriptive, recognising that each school is unique and thus should be given autonomy and ownership (63, 64). They assert:

1. Individual schools must develop programs to protect children from bullying in consultation with students and parents.
2. Schools must include guidelines for reporting, intervening and accessing help for students, parents, carers and teachers.
3. Parents must be informed of the programs and encouraged to be proactive.
4. Schools are encouraged to use evidence-based practices to develop and implement programs.
5. Statistics should be kept.
6. Programs must be reviewed regularly.

Key contacts for the school in relation to these policies are the school principal or the school network leader.

**Professional Medical Bodies' Recommendations**

The Royal Australian College of General Practitioners (RACGP) recognises the importance of early intervention in preventing adverse health outcomes (65). As children of all ages visit their general practice, on average, once or more a year (66), general practitioners are in a position to see change in individual children, screen for bullying behaviour and initiate treatment and preventative measures (67). The RACGP recommend a number of health checks be performed in children presenting at different ages. In early life, they recommend assessing the family environment, child-parent relationship, and developmental and behavioural progress. Based on these, appropriate advice and counselling should be given. In a child’s school years, the general practitioner should discuss how the child is progressing at school, and intervene with social and emotional well-being counselling before signs, such as of depression, are evident. Children 12 years old and over should be screened for depression (65, 68).

The Australian Medical Association (AMA) also advocates anti-bullying policies and awareness and has produced two documents: one to help guide doctors in dealing with childhood bullying (69); and another aimed at children (70). They assert the notion that doctors are trusted by the community and are in a position to discuss bullying with children and, therefore, encourage children to see a doctor about these issues. This discussion may be informal, require multiple consultations and involve the child’s family. If the school is a factor, the AMA recommends encouraging the family to talk to the school. However, if the school has inadequate resources to deal with the issue, it could be appropriate to refer a child to other professionals such as psychologists, youth workers and social workers.

**Strategies for General Practice**

Strategies that can be implemented in a general practice to reduce bullying based behaviour in children are summarised in Table 2. These strategies are based on the SNAP framework for general practice (71). Justification, evidence, references, level of protection and the primary people responsible for each strategy are given. Many strategies only require simple changes and additions to the existing protocols, practices and infrastructure of a general practice. They complement existing community programs, including the central role of local schools, and leverage on the position of the practice in the community.

**Conclusion**

Bullying is a complex socio-cultural phenomenon (72) and this is reflected in the quality of, and variation in, the published studies. It is interesting to note that despite Australian governments investing much time and effort into the problem, individual schools are essentially left to develop their own programs (63, 64). While this supports studies showing that anti-bullying programs are more likely to succeed if schools are given autonomy and are free to adapt programs to their unique needs (2), it makes it difficult to evaluate, and therefore improve, such programs. Despite this, the existing programs and policies are believed to be responsible for the recent decrease seen in bullying seen in many countries (73). Given the position of the general practice in the community, it can also make a valuable contribution in further reducing the prevalence of bullying behaviour and its serious life-long detrimental effects.

**Acknowledgements:** nil

**Conflicts of interest:** none to declare

**Stock image:** WikiMedia Commons

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Efficacy of semi-urgent ECG exercise stress testing in patients referred from the Emergency Department with chest pain

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Introduction

A patient presenting to the emergency department (ED) with chest pain is a common encounter. In 2008-2009 in Australia, chest pain was the seventh most common Australian Refined-Diagnosis Related Group causing same-day acute separations and second most common causing overnight acute separations at public hospitals (1). “Pain in throat and chest” was the top principal diagnosis for overnight acute separations in public and private hospitals combined in Australia in 2008-2009 (1). This shows that patients presenting with chest pain frequently result in overnight admissions to hospital. Thus, efficient screening and admission processes are necessary for patients presenting with chest pain.

The primary concern of patients and physicians is whether the chest pain indicates an acute coronary syndrome (ACS), such as acute myocardial infarction (AMI) or unstable angina. The benefit of accurately identifying and rapidly managing ACS is known (2), and inadvertent discharge of patients with undiagnosed ACS is associated with significant mortality and life-threatening complications (3-5). However, the rate of missed ACS diagnosis is low (3-4) and a good initial history and clinical assessment including ECG and cardiac biomarker measurement can determine which patients have a less than 1% risk of developing major complications, and less than 5% risk of having an AMI (6-8). Therefore with the high volume of patients presenting with chest pain, and only a minority having life-threatening conditions (8) it is also important to identify those without serious complications early, and reduce unnecessary admission and investigation of this population, with its associated cost to the hospital system (5).

An efficient diagnostic algorithm is needed to assess patients presenting with chest pain (5, 9) to ensure accurate diagnosis of those with ACS, and guide management for those at lower risk.

An exercise stress test (EST) is commonly used to diagnose or rule-out coronary artery disease (CAD) in patients that present with chest pain who are at low risk of having an ACS (10). If coronary blood flow is obstructed and cannot meet the increased metabolic demand, myocardial ischaemia occurs (11). ESTs aim to induce myocardial ischaemia through exercise, and thus prove coronary artery obstruction. Many studies have demonstrated the safety of ESTs (6-8, 11) and they may now be performed after 6-8 hours observation after presentation with chest pain, if the patient is at low-to-intermediate probability of ACS (8). The sensitivity and specificity of EST is variably stated around 70-78% and 70-75% respectively (8, 10). Thus, for EST to be used as a diagnostic procedure, the pre-test probability of CAD must be taken into account. In a low risk population, a positive result is more likely to be a false

Abstract

Objective: To analyse the efficacy of exercise stress test (EST) referral of patients presenting to the emergency department (ED) with chest pain.

Design, setting and patients: Retrospective, observational study of consecutive patients undergoing EST between June 2009 and March 2011 at a tertiary Canberra public hospital.

Main outcome measures: EST result, time between presentation and performing EST, risk factor profile, reason for referral, and further presentation to ED after EST.

Results: 326 ESTs were performed between June 2009 and March 2011. 5.7% were positive for inducible myocardial ischaemia. Most (92.0%) were performed more than 72 hours after initial presentation. No patients under 46 returned a positive result. Hypertension was associated with inducible myocardial ischaemia (OR 4.925, 95%CI 1.073–22.596) as was presence of diabetes (OR 5.625, 95%CI 1.784–17.733). No other risk factors were predictive. The most common reasons for referral were “chest pain/discomfort at rest, in last 48 hours” (76.2%) and “two or more risk factors” (62.9%). The intermediate risk factors associated with inducible myocardial ischaemia were “known CAD” (OR 3.000, 95%CI 0.866–10.387) and “age greater than 65” (OR 4.343, 95%CI 1.431–13.181). 6.7% of patients returned to ED with a cardiac complaint within six months after EST.

Conclusions: ESTs are not being performed within the recommended time frame. Reduction of inappropriate and unnecessary referrals could help remedy this. Patient risk factor profile is not useful to predict inducible myocardial ischaemia in the acute setting. Increasing patient age is likely to be the best predictor.
positive, but in a high risk population, a negative result cannot rule out isch-aemic heart disease (IHD). EST has the greatest diagnostic meaning when used in patients with an intermediate pre-test probability of CAD (10, 12).

In The Canberra Hospital (TCH) ACT, patients presenting to the ED with chest pain who are considered at intermediate risk for ACS may be referred for an outpatient exercise stress test. This assessment is based on the history and risk factors the patient has, combined with ECG findings and negative serial cardiac biomarkers that rule out ACS. Relevant parts of the history are: hypercholesterolaemia, hypertension, primary relatives with early-onset IHD, a history of smoking, diabetes, obesity or prior cardiac disease and treatment. The intermediate risk factors are: chest pain/discomfort at rest within last 48 hours (but currently resolved), new onset angina less than two weeks ago, known coronary artery disease, age greater than 65 years, two or more risk factors, presence of known diabetes with atypical ACS symptoms or presence of chronic kidney disease with atypical ACS symptoms (13). Outpa-tient stress testing is supported as safe and useful, but only if it is performed within 72 hours of discharge, preferably within 24 (8, 13-14). However, it is known that testing may not occur on time or at all, due to difficulties with follow-up and patient compliance (8, 15-16).

It is known that many ESTs in TCH are being performed more than 72 hours after initial presentation (unpublished data). This project aims to analyse the efficacy of EST referral for patients presenting to the emergency department with chest pain. The risk factors and criteria used to determine which patients are at intermediate risk and appropriate for referral will be evaluated.

Methods

Data was collected for all patients referred from ED for EST in the Cardiology department of TCH from June 2009-March 2011. The medical records of these patients were accessed and the results of EST were analysed. The EST referral sheets were analysed

Table 1. Patient demographics and risk factor burden frequencies organised by result of EST.

<table>
<thead>
<tr>
<th></th>
<th>Positive (%)</th>
<th>Negative (%)</th>
<th>Equivocal (%)</th>
<th>Row Total (% of total*)</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>12 (5.8)</td>
<td>122 (58.7)</td>
<td>74 (35.6)</td>
<td>208 (66)</td>
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</tr>
<tr>
<td>Female</td>
<td>6 (5.5)</td>
<td>68 (62.4)</td>
<td>35 (32.1)</td>
<td>109 (34)</td>
<td>0.809</td>
</tr>
<tr>
<td>Age Groups</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>26-35</td>
<td>18 (5.7)</td>
<td>190 (59.9)</td>
<td>109 (34.4)</td>
<td>317 (100)</td>
<td></td>
</tr>
<tr>
<td>36-45</td>
<td>12 (5.8)</td>
<td>122 (58.7)</td>
<td>74 (35.6)</td>
<td>208 (66)</td>
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<tr>
<td>46-55</td>
<td>6 (5.5)</td>
<td>68 (62.4)</td>
<td>35 (32.1)</td>
<td>109 (34)</td>
<td>0.809</td>
</tr>
<tr>
<td>&gt;75</td>
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<td>0 (0)</td>
<td>12 (75.0)</td>
<td>16 (5.0)</td>
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</tr>
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<td>48 (16.7)</td>
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<tr>
<td>Atypical</td>
<td>11 (4.6)</td>
<td>156 (65.3)</td>
<td>72 (30.1)</td>
<td>239 (83.3)</td>
<td>&lt;0.001</td>
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<td>Risk Factors</td>
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<td></td>
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<td>Hypercholesterolaemia</td>
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<td>9 (6.4)</td>
<td>84 (59.6)</td>
<td>48 (34.0)</td>
<td>141 (49.3)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>8 (7.3)</td>
<td>66 (60.6)</td>
<td>35 (32.1)</td>
<td>109 (38.1)</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>15 (9.3)</td>
<td>86 (53.1)</td>
<td>61 (37.7)</td>
<td>162 (56.7)</td>
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</tr>
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<td>No</td>
<td>2 (1.7)</td>
<td>81 (70.4)</td>
<td>32 (27.8)</td>
<td>115 (40.2)</td>
<td>0.003</td>
</tr>
<tr>
<td>Family History</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5 (5.7)</td>
<td>55 (62.5)</td>
<td>28 (31.8)</td>
<td>88 (30.8)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>10 (5.8)</td>
<td>102 (59.3)</td>
<td>60 (34.9)</td>
<td>172 (60.1)</td>
<td>0.877</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1 (2.2)</td>
<td>26 (57.8)</td>
<td>18 (40.0)</td>
<td>45 (15.7)</td>
<td></td>
</tr>
<tr>
<td>Quit&lt;1yr ago</td>
<td>0 (0)</td>
<td>6 (60.0)</td>
<td>4 (40.0)</td>
<td>10 (3.5)</td>
<td></td>
</tr>
<tr>
<td>Quit&gt;1yr ago</td>
<td>7 (8.1)</td>
<td>46 (53.5)</td>
<td>33 (38.4)</td>
<td>86 (30.1)</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>9 (6.2)</td>
<td>94 (64.8)</td>
<td>42 (29.0)</td>
<td>145 (50.7)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>10 (4.2)</td>
<td>146 (61.6)</td>
<td>81 (34.2)</td>
<td>237 (82.9)</td>
<td>0.198</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>0 (0)</td>
<td>5 (62.5)</td>
<td>3 (37.5)</td>
<td>8 (2.8)</td>
<td></td>
</tr>
<tr>
<td>Oral Meds</td>
<td>5 (17.2)</td>
<td>15 (51.7)</td>
<td>9 (31.0)</td>
<td>29 (10.1)</td>
<td></td>
</tr>
<tr>
<td>Diet</td>
<td>2 (16.7)</td>
<td>6 (50.0)</td>
<td>4 (33.3)</td>
<td>12 (4.2)</td>
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<tr>
<td>T2DM</td>
<td>7 (17.1)</td>
<td>21 (51.2)</td>
<td>13 (31.7)</td>
<td>41 (14.3)</td>
<td>0.006</td>
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<tr>
<td>Obesity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4 (3.8)</td>
<td>62 (58.5)</td>
<td>40 (37.7)</td>
<td>106 (37.1)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>13 (7.2)</td>
<td>110 (61.1)</td>
<td>57 (31.7)</td>
<td>180 (62.9)</td>
<td>0.344</td>
</tr>
<tr>
<td>Past Medical History</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior Coronary Angiogram</td>
<td>5 (10.0)</td>
<td>23 (46.0)</td>
<td>22 (44.0)</td>
<td>50 (17.5)</td>
<td>0.064</td>
</tr>
<tr>
<td>Prior PTCA</td>
<td>2 (7.4)</td>
<td>15 (55.6)</td>
<td>10 (37.0)</td>
<td>27 (9.4)</td>
<td>0.862</td>
</tr>
<tr>
<td>Prior MI</td>
<td>4 (11.8)</td>
<td>15 (44.1)</td>
<td>15 (44.1)</td>
<td>34 (11.9)</td>
<td>0.081</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>2 (8.6)</td>
<td>3 (42.9)</td>
<td>2 (28.6)</td>
<td>7 (2.4)</td>
<td>0.037</td>
</tr>
</tbody>
</table>

*: total where results available including EST results, i.e. 286 for risk factors with EST.
when available to identify the risk factor criteria used to refer patients. If any risk factors were left blank (not marked by the referring doctor) they were assumed to be absent for that patient. The presenting complaint as recorded on each EST referral was stratified into typical or atypical of ACS, as indicated by the cardiologist on the EST summary sheet. The association between risk factors and EST outcomes were measured. Statistical analyses were performed using SPSS software, version 15 (SPSS Inc, Chicago, Ill, USA). P<0.05 was considered statistically significant. A survey was developed in an attempt to obtain a prospective follow up of patients who had been referred for EST after presenting with chest pain to the emergency department. However, due to lack of participation this was abandoned. A retrospective follow up was performed by accessing the medical records as above, to check for re-presentation to the ED within six months of EST, for all patients tested between June 2009-February 2011. These patients were classified as those who returned with a cardiac complaint, or with an unrelated, non-cardiac condition based on ED discharge sheets. Ethics approval was granted for this project by the ACT-Health Human Research Ethics Committee.

Results

Patient Demographic:
From June 2009-March 2011 326 ESTs were performed on patients referred with chest pain from the Emergency Department of TCH. EST results were available for 317. Of these, 208(66%) were male and 109(34%) were female (Table 1). The mean age of patients tested was 55.2 years(SD=11.6) and age ranged from 14-83 years old.

Results of EST:
Of the 317 ESTs with results available, 18(5.7%) were positive for inducible myocardial ischaemia, 190(59.9%) were negative, and 109(34.4%) were equivocal. There was no significant difference in EST results between males and females. The most positive results were from the age group 56-65(7, 8.3%) but the highest proportion of positive results were from the age group over 75(4, 25.0%) (Table 1). There were no positive test results for patients less than 46 years old.

The length of time between patients presenting to the Emergency Department and performing an EST was on average 26 days(SD=26.3), and ranged from 0-195 days. The median time between presentation and testing was 7 days (Figure 1). Excluding outliers that performed EST more than 50 days after presentation the time between presentation and performing EST was on average 16.9 days(SD=13.5) (Figure 2). The majority of all tests (58.9%) are performed within three weeks of presentation, while a minority (8.0%) are performed within 72 hours (Table 2). Of those patients being tested more than three weeks after presentation, 5.3% were still obtaining a positive result (Table 3).

Risk Factor Burden of Patient Population:
Risk factor profile data was available for 290 of the patients performing EST. The most common risk factors were hypertension(163 cases, 56.2%), hypercholesterolaemia(143, 49.3%) and any smoking history(142, 49.0%) (Table 4).

Patients with hypertension had more positive ESTs than those without.
Table 2. Data for time length between initial presentation to Emergency and performance of an EST for all patients.

<table>
<thead>
<tr>
<th>Time between presentation and performance of EST</th>
<th>Count (%)</th>
<th>Cumulative %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Same Day</td>
<td>3 (0.9)</td>
<td>0.9</td>
</tr>
<tr>
<td>24 – 72 hours</td>
<td>23 (7.1)</td>
<td>8.0</td>
</tr>
<tr>
<td>72 hours – 1 week</td>
<td>58 (17.8)</td>
<td>25.8</td>
</tr>
<tr>
<td>1 - 2 weeks</td>
<td>77 (23.6)</td>
<td>49.4</td>
</tr>
<tr>
<td>2 - 3 weeks</td>
<td>31 (9.5)</td>
<td>58.9</td>
</tr>
<tr>
<td>More than 3 weeks</td>
<td>134 (41.1)</td>
<td>100.0</td>
</tr>
<tr>
<td>Total</td>
<td>326 (100)</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Table 3. Data for time length between initial presentation to Emergency and performance of EST correlated with EST results (for those patients with results available).

<table>
<thead>
<tr>
<th>Time between presentation and performance of EST</th>
<th>EST Result</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive (%)</td>
</tr>
<tr>
<td>Same Day</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td>24 – 72 hours</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>72 hours – 1 week</td>
<td>2 (3.5)</td>
</tr>
<tr>
<td>1 – 2 weeks</td>
<td>2 (2.8)</td>
</tr>
<tr>
<td>2 – 3 weeks</td>
<td>6 (19.4)</td>
</tr>
<tr>
<td>More than 3 weeks</td>
<td>7 (5.3)</td>
</tr>
<tr>
<td>Total</td>
<td>18 (5.7)</td>
</tr>
</tbody>
</table>

Table 4. Risk Factor frequency in the whole patient population, (where data was available).

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Yes (%)</th>
<th>No (%)</th>
<th>Unknown (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercholesterolaemia</td>
<td>143 (49.3)</td>
<td>109 (37.6)</td>
<td>38 (13.1)</td>
<td>290</td>
</tr>
<tr>
<td>Hypertension</td>
<td>163 (56.2)</td>
<td>118 (40.7)</td>
<td>9 (3.1)</td>
<td>290</td>
</tr>
<tr>
<td>Family History (IHD in primary relative &lt;55)</td>
<td>88 (30.3)</td>
<td>176 (60.7)</td>
<td>26 (9.0)</td>
<td>290</td>
</tr>
<tr>
<td>Smoking</td>
<td>142 (49.0)</td>
<td>148 (51.0)</td>
<td></td>
<td>290</td>
</tr>
<tr>
<td>Diabetes</td>
<td>51 (17.6)</td>
<td>239 (82.4)</td>
<td></td>
<td>290</td>
</tr>
<tr>
<td>Obesity</td>
<td>108 (37.2)</td>
<td>182 (62.8)</td>
<td></td>
<td>290</td>
</tr>
<tr>
<td>Past Medical History</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior Coronary Angiogram</td>
<td>50 (17.2)</td>
<td>240 (82.8)</td>
<td></td>
<td>290</td>
</tr>
<tr>
<td>Prior PTCA</td>
<td>27 (9.3)</td>
<td>263 (90.7)</td>
<td></td>
<td>290</td>
</tr>
<tr>
<td>Prior MI</td>
<td>34 (11.7)</td>
<td>256 (88.3)</td>
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<td>290</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>7 (2.4)</td>
<td>283 (97.6)</td>
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<td>290</td>
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<tr>
<td>Intermediate Risk Factor</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest pain/discomfort at rest &lt;48hrs</td>
<td>218 (76.2)</td>
<td>68 (23.8)</td>
<td></td>
<td>286</td>
</tr>
<tr>
<td>New onset angina (&lt;2 weeks)</td>
<td>52 (18.2)</td>
<td>234 (81.8)</td>
<td></td>
<td>286</td>
</tr>
<tr>
<td>Known CAD</td>
<td>32 (11.2)</td>
<td>254 (88.8)</td>
<td></td>
<td>286</td>
</tr>
<tr>
<td>Age&gt;65yrs</td>
<td>54 (18.9)</td>
<td>232 (81.1)</td>
<td></td>
<td>286</td>
</tr>
<tr>
<td>2 or More Risk Factors</td>
<td>180 (62.9)</td>
<td>106 (37.1)</td>
<td></td>
<td>286</td>
</tr>
<tr>
<td>Known Diabetes (with atypical symptoms of ACS)</td>
<td>27 (9.4)</td>
<td>259 (90.6)</td>
<td></td>
<td>286</td>
</tr>
<tr>
<td>Known Chronic Kidney Disease (with atypical symptoms of ACS)</td>
<td>7 (2.4)</td>
<td>279 (97.6)</td>
<td></td>
<td>286</td>
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</table>

(p<0.005) (Table 1) and greater odds of a positive EST result, OR=4.925 (95%CI 1.073–22.596). Patients with known diabetes controlled with oral medication or diet were grouped as “Type II Diabetes Mellitus” and it was shown these patients were more likely to obtain a positive EST result, OR=5.625 (95%CI 1.784–17.733). The other risk factors showed no significant relationship with EST result (Table 1).

50(17.2%) patients had a prior coronary angiogram, 34(11.7%) had a prior MI, 27(9.3%) had prior PTCA and 7(2.4%) had a prior CABG. Generally patients with prior cardiac intervention had a higher proportion of positive EST results, but the small sample sizes resulted in borderline statistically significant relationships (Table 1).

Intermediate Risk Factors for Referral:
Intermediate risk factors used for referral were available for 286 patients. The most common were “chest pain/discomfort at rest” with 218(76.2%) and “two or more risk factors” with 180(62.9%) (Table 4).

Those referred with known presence of CAD had three times greater odds of receiving a positive result than those without, OR=3.000 (95%CI 0.866–10.387). Patients over 65 years old were also more likely to have a positive result than those under 65 OR=4.343 (95%CI 1.431–13.181) (Table 5).

Of 289 patients with available data, 48 (16.6%) were referred with a presenting complaint typical of ACS. A higher proportion of patients had a positive result when presenting with a complaint typical of ACS (6, 12.5%) than those with an atypical complaint (11, 4.6%) OR=3.416 (95%CI 1.064-10.966) (p<0.001) (Table 1).
Table 5. Intermediate risk factors used for referral and correlation with EST results.

<table>
<thead>
<tr>
<th>Intermediate Risk Factor</th>
<th>EST Result</th>
<th></th>
<th></th>
<th></th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive (%)</td>
<td>Negative (%)</td>
<td>Equivocal (%)</td>
<td>Row Total (% of Total)</td>
<td></td>
</tr>
<tr>
<td>Chest pain at rest</td>
<td>11 (5.1)</td>
<td>135 (62.5)</td>
<td>70 (32.4)</td>
<td>216 (76.6)</td>
<td>0.281</td>
</tr>
<tr>
<td>New Onset Angina</td>
<td>3 (5.8)</td>
<td>32 (61.5)</td>
<td>17 (32.7)</td>
<td>52 (18.4)</td>
<td>0.979</td>
</tr>
<tr>
<td>Known CAD</td>
<td>5 (15.6)</td>
<td>13 (40.6)</td>
<td>14 (43.8)</td>
<td>32 (11.3)</td>
<td>0.012</td>
</tr>
<tr>
<td>Age&gt;65yrs</td>
<td>7 (13.5)</td>
<td>18 (34.6)</td>
<td>27 (51.9)</td>
<td>52 (18.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥2 Risk Factors</td>
<td>14 (7.9)</td>
<td>100 (56.2)</td>
<td>64 (36.0)</td>
<td>178 (63.1)</td>
<td>0.091</td>
</tr>
<tr>
<td>Known Diabetes</td>
<td>1 (4.0)</td>
<td>16 (64.0)</td>
<td>8 (32.0)</td>
<td>25 (8.9)</td>
<td>0.872</td>
</tr>
<tr>
<td>Known CKD</td>
<td>1 (14.3)</td>
<td>4 (57.1)</td>
<td>2 (28.6)</td>
<td>7 (2.5)</td>
<td>0.644</td>
</tr>
</tbody>
</table>

Table 6. Number of patients who presented to the emergency department within six months of performing EST and correlation with their result.

<table>
<thead>
<tr>
<th>Reason for return to hospital</th>
<th>EST Result</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive (%)</td>
<td>Negative (%)</td>
<td>Equivocal (%)</td>
<td>Row Total (% of Total 299 patients)</td>
</tr>
<tr>
<td>Cardiac complaint</td>
<td>2 (10.0)</td>
<td>7 (35.0)</td>
<td>11 (55.0)</td>
<td>20 (6.7)</td>
</tr>
<tr>
<td>Unrelated condition</td>
<td>3 (6.7)</td>
<td>22 (48.9)</td>
<td>20 (44.4)</td>
<td>45 (15.5)</td>
</tr>
</tbody>
</table>

Follow-up:
Follow-up was performed on patients who performed EST between June 2009-February 2011 (308 patients). Data was available for 299, of these 65 (21.7%) re-presented to ED within six months. 20 (30.8%) of these patients presented with a cardiac complaint, while the other 45 (69.2%) were for unrelated conditions. Thus, 6.7% of patients performing EST returned to the emergency department with a cardiac complaint within six months (Table 6).

Discussion
To our knowledge this study represents the largest retrospective analysis of patients performing EST at TCH. We found a low, but significant rate of detection of inducible myocardial ischaemia. Most patients being referred for EST are not completing the EST within the recommended timeframe, and EST referral should be reviewed. This study showed that almost all (92.0%) patients being referred for outpatient EST are not performing them within the recommended 72 hour time frame. Low patient compliance and lack of knowledge of importance of EST may be reasons patients delay performance of EST (15-16). This could be managed by booking ESTs from the ED (15-16). A previous study at TCH has shown the primary reason for patients failing to perform EST within 72 hours is that no appointments are available within that time frame (unpublished data). This is due to the limited number of qualified staff and resources available, combined with a large number of EST referrals. Ensuring appropriate referral of patients can ensure EST performance occurs in the recommended time frame. Multiple patients were detected with inducible myocardial ischaemia more than three weeks after their initial presentation. This is concerning, as lack of early access to EST means these patients may have underlying, undiagnosed CAD and are at risk of a cardiac event after discharge from the ED.

The rate of detection of 5.7% is similar to the positive EST rate in other studies of low-risk patient populations[6, 14, 17]. This low rate of detection may suggest that most patients being referred for EST are actually low-risk for ACS, not intermediate. This can reduce the efficacy of EST as a diagnostic test, with a higher rate of false positives in a low-risk patient population.

The most commonly used ‘intermediate risk factor’ to refer patients was “chest pain/discomfort at rest” however the nature of the chest pain is important, with presenting complaints typical of ACS more predictive of a positive result. This contradicts a study by Hermann et al (2010) which showed patients with typical angina were no more likely to have inducible myocardial ischaemia on EST than patients with other presenting complaints (18). A meta-analysis showed that while certain features of the chest pain history increased the likelihood of ACS, none were sufficiently powerful to warrant discharge of the patient (19). Some presenting complaints of atypical “chest pain” are distinctly non-cardiac in origin. The frequency of this was not analysed in this study, but other studies have shown as much as 55% of patients presenting to ED with “chest pain” have non-cardiac problems (4).

The only patient risk factors associated with inducible myocardial ischaemia were: hypertension, and type 2 diabetes mellitus. It should be noted that the above two associations are significant, but due to the small sample size, it was difficult to demonstrate precise associations and caution should be taken with their interpretation. Multiple studies show that cardiac risk factors can help determine the likelihood of a long term coronary event, but are not useful in diagnosing ACS in the acute setting (8, 17, 20-23). Thus, the inclusion of cardiac risk factors such as hypercholesterolaemia and obesity may result in a greater number of unnecessary EST referrals.

Clarifying the intermediate risk factors used for referral on the EST referral documents may reduce the number of unnecessary referrals. The most used criteria for referral “chest pain/discomfort at rest” should be limited to typical cardiac pain to reduce the number of referrals for non-cardiac pain. The second most used criteria “two or more risk factors” may be misleading as cardiac risk factors do not play a role in determining the likelihood of acute myocardial ischaemia.
Patients more than 65 years old had greater odds of inducible myocardial ischaemia, OR 4.343 (95%CI 1.431–13.181). Increasing patient age is possibly the best predictor of inducible myocardial ischaemia, as indicated by the increasing proportion of positive EST results with increasing age (Table 1). Additionally, no positive EST results were obtained in patients who were younger than 46 years old (14.7% of cases). This is confirmed by other studies showing that testing patients under 40 years of age is not useful (24-25). Eliminating the unnecessary testing of these patients would reduce the burden of referrals and may make EST more accessible to patients at greater risk.

A substantial number of patients are referred for EST for whom the test is completely inappropriate. Of the 326 referrals, 40(12.3%) were marked as inappropriate. The most common reasons a referral for EST was inappropriate were: patient had resting ECG abnormalities, patient still taking medication (i.e. β-blockers) and patient was unable to exercise. The inappropriate referral of these patients prevents other patients from accessing EST in the recommended time frame and should be ceased.

The follow up data revealed a relatively low rate of cardiac complication after EST, compared with other studies (26). This demonstrates the safety of the outpatient EST process, despite performance outside the recommended guidelines. However, a significant limitation of this study is the minimal follow up that was possible for all patients, preventing analysis of adverse cardiac events post-EST. Future studies with extensive follow up would be beneficial to determine the true rate of CAD detected or missed by outpatient EST and the risk of false positive results. Patients with positive or equivocal results could qualify for further investigation through stress echocardiography, CT-coronary angiography or coronary angiography based on their risk profile for CAD. Patients with negative initial EST could be monitored long-term for future cardiac complaints or hospital presentations.

To manage the high number of patients presenting with “chest pain” and its associated complexities, many hospitals are moving to an accelerated diagnostic protocol for evaluating low-risk patients. These are run through specialised chest pain units, and aim to rapidly risk stratify patients, to allow early and safe discharge, on the basis of early performance of EST (8, 27-28). Establishment of a chest pain unit at TCH could allow for performance of more ESTs within the recommended time frame and lead to better patient outcomes. This would require a significant investment in facilities and trained staff, to ensure ESTs are more regularly available, and may be worthwhile if supported by further research and analysis.

Competing interests: none identified.

References:

LITERATURE REVIEW

Vitamin C for preventing and treating the common cold: a review of the implications on clinical practice and patient-centred care

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The common cold is responsible for eleven percent of all general practitioner consultations annually in Australia (1). Vitamin C has been used since the 1930’s by doctors and patients alike to alleviate symptoms and/or reduce the duration of the illness, despite uncertainty regarding the benefits. The social implications of time off work, medical costs, and associated discomforts highlight the need for doctors to ensure that evidence-based recommendations regarding Vitamin C are given to patients. Given the burden of the common cold on society, this review aims to evaluate current literature on Vitamin C, to answer the question of whether or not this supplement has a role in modern clinical practice.

Chalker and Hemilä’s 2013 systematic review aimed to determine whether vitamin C reduced the incidence, duration or severity of the common cold when used as either a regular supplement or a therapeutic treatment (2). This comprehensive review consists of predominantly randomized double-blind trials in which over 20,000 adult patients were subjected to differing vitamin C dosages at varying time periods before the onset of cold symptoms. The trials found that daily supplementation of Vitamin C had no effect on incidence. There was however a “modest but consistent” effect on decreasing the duration of the common cold. Trials also found that the duration could be halved when given to adults subject to high physical exertion (such as marathon runners). These particular trials had small sample sizes and require further research to validate the findings. Exclusion of the non-randomized, non-double-blind trials did not have a statistically significant effect on the outcomes. Thus, Chalker and Hemilä concluded that the slight benefits to duration suggest “it may be worthwhile” for patients to either take daily supplements, or test whether therapeutic supplementation works for them (2).

The overall safety and potential benefits to other diseases will also influence a clinician’s decision to prescribe vitamin C. Peer-reviewed literature assessing vitamin C has determined that the supplement can be taken daily, in large doses and in conjunction with other medications without any detriment to the patient (2). A small number of cases of vitamin C-related health problems have been reported, however in each of these situations physicians later concluded that adverse effects on the patients were due to other health problems and not vitamin C supplementation (5). Vitamin C deficiencies are prevalent in smokers, the elderly and people from low socioeconomic areas, particularly in developing nations such as India (6,7). This is cause for concern due to the vital roles it plays in the body as a cofactor to eight different enzymes and as a powerful antioxidant (8). Reports outline how maintaining sufficient vitamin C levels prevent multiple deficiency disorders such as scurvy (9). Intravenous use of vitamin C might also play a role in antitumor activity (10). These findings provide another justification for doctors to recommend regular supplementation, however do not strengthen the argument for providing vitamin C for treatment of the common cold in non-vitamin C deficient patients. Sackett et al. highlight how modern doctors must integrate evidence with clinical expertise and patient values in order to provide universal care to their patient (3). As there is no cure for the common cold, only symptomatic medication can be given to patients (1). Systematic reviews conducted to determine the efficacy of over the counter (OTC) medications such as antihistamines, decongestants and analgesics found that combinations of the aforementioned drugs decreased the severity of symptoms such as rhinorrhea, cough and sneezing, allowing patients to assume daily activities sooner (4). The inclusion of these prescriptions in treatment plans considerably lessens vitamin C’s role in decreasing cold symptoms.

Current literature potentially suggests that vitamin C’s modest benefits to the duration of the cold have wider social and economic effects. A randomized study conducted in Sweden by Hellgren et al. found that the common cold can be attributed to a net productivity loss of €2.7 billion ($AUD 3.5 billion) annually (11); it can be assumed that developed nations with larger populations would have even higher annual losses in productivity. Hellgren...
et al. concluded that a reduction of cold symptoms by one day per individual would save up to €528 million ($AUD 678 million) yearly (11). This can be corroborated by a similar study conducted in the United States by Fendrick et al. which estimated that the cost of physician visits, OTC medications and lost productivity from missed school and work days was roughly USD 20 billion ($AUD 19.6 billion) (12). The same study found that the common cold can be attributed to forty percent of all time lost from work. Chalker and Hemilä determined that when vitamin C was administered, the duration of the common cold was reduced in adults on average by eight percent, and by fourteen percent in children (2). Arrol (2011) states that the average prognosis of symptoms lasts one week, which amounts to the cold lasting thirteen hours less in adults, and twenty-three hours less in children if vitamin C is regularly used (1). As such, what superficially seems like a small benefit to the individual may actually amount to much larger societal benefits, warranting its consideration as a treatment. The above trials involved telephone and mail surveys, only one of which was randomised. More stringent testing of these conclusions would provide significantly stronger support for Vitamin C supplementation.

Doctors need to present the pros and cons of vitamin C to their patients before agreeing on its inclusion in treatment plans. Given the relatively small benefits exhibited by vitamin C supplementation, the cost to the individual of implementing this treatment in underdeveloped and low economic areas may not be justified. It is incumbent upon medical practitioners to determine whether or not regular supplementation is necessary for that patient’s lifestyle. In the case of vitamin C, this means that doctors would only be likely to achieve positive outcomes from patients who regularly have cold symptoms, cannot afford lost productivity from being sick, or who undergo extreme physical strain. In order for patients to receive the optimal health outcomes, they must be presented with the findings of current common cold treatment methods and discuss their desires, expectations and beliefs with their medical practitioners. If there is a difference of opinion, it is up to the doctor to attempt to explain their perspective and present the supporting evidence in a way that the patient can understand. It is important to note however that the patients are ultimately the ones who have to guide treatment decisions; if doctors breach the patient’s right to autonomy and start showing paternalistic traits, they risk fostering distrust, losing rapport and developing a dependence on the health system (16).

Health practitioners should be aware that the primary medical treatment methods prescribed for the common cold are aimed at symptomatic relief and should include analgesics, decongestants and antihistamines. Chalker and Hemilä found that vitamin C does provide some advantage to the common cold, has wider societal benefits, is safe and prevents other health problems (2), thus providing scope for doctors to be recommending that their patients be regularly taking vitamin C. Medical practitioners need to be judicial in their treatment decisions, based on their consideration of the patient’s circumstances and what is ultimately going to benefit the individual the most. Due to the individual and societal benefits achieved from administering vitamin C for the common cold, this supplement does have a place in modern clinical practice.

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Conflicts of interest: none to declare

Stock image: WikiMedia Commons

References:


Childhood Immunisation and Parental Education Levels: A Comparative Survey across 50 Years

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Abstract

Background: Many authors have found an association between immunisation rates and parental educational levels. However, few studies have quantified the degree of risk that increases with each decrease in educational level. Nor have there been any studies which have assessed whether the same level of education once held five decades ago holds the same risk for non-immunisation as it does in current society. This study aims to clarify these issues.

Method: A retrospective analysis based on a survey of 1033 adults living in Australia across two groups aged 18-30 years (young group) and 70-95 years (old group) was conducted in March 2012 and 2013. Information on the number of childhood immunisations and the parental educational level, as well as other socio-demographics (e.g. education, number of siblings) were collected.

Results: Across both age groups, we found that the vaccination rate in childhood was significantly proportional to the parental educational level. In the young group, a decrease in educational level from a tertiary to a TAFE education significantly increases the risk of low immunisation status by approximately 5 times (p<0.01). In the old group, a decrease in educational level from tertiary to primary education increases the risk of low immunisation by approximately 3 times (<0.05).

Conclusions: Our data indicates that, in current society, interventions designed to increase immunisation rates need to target parental populations who hold an education level of TAFE and lower.

Introduction

Low immunisation coverage in children poses a silent but potentially catastrophic risk in the community. Although numerous studies have examined a number of socio-demographic predictors for non-vaccination, the level of immunisation has always been found to be positively associated with the level of education of the parents or the head of the household (1-4).

In the past eight decades, the proportion of fully immunised children aged 0-6 years has increased dramatically in Australia, from 55% in 1983 to 71% in 1989-90, and 91.8% in 2013 (5). Moreover, in the past eight decades, the education system and number of tertiary graduates in Australia has improved dramatically. Could this increase in immunisation be a result of the increased proportion of Australia’s population being tertiary educated? Or have changes in Australian policy, such as the requirement of immunising one’s child in order to receive a Centrelink family payment, made people with lower socioeconomic status more likely to be vaccinated? Hence it remains unclear as to whether parental education is still associated with immunisation, and if so, to what degree. Understanding the changing pattern of association may help predict future changes with increased tertiary graduates as well as serve as a model for other countries where the number of tertiary educated parents is in its early stages.

An epidemiological study was conducted in regional New South Wales, Australia to identify any intrinsic association between the levels of vaccination and the parental educational background. Comparison between an older and younger group’s experience of immunisation as children was used to illustrate the changing impact of parental educational background over the past several decades. We hypothesised that in both groups, participants with parents or carers with higher levels of education were more likely to be immunised.
Furthermore, we hypothesised that the increase in risk for low immunisation status in the secondary educated compared to tertiary educated, would be far greater in the younger group than the older group due to the increasing proportion of tertiary educated individuals in the population.

Methodology

Data collection
The study data was collated from two surveys administered in March 2012 and March 2013 by second year medical students from the University of New South Wales (UNSW), Sydney, Australia. This study was primarily an educational project, where groups of second year medical students develop and analyse their own research question using data obtained collectively. Each second year medical student was instructed to interview and complete a questionnaire for two subjects; one 18-35 years of age and another 75-90 years of age (as of the year in which interviewed). Subjects were required to speak fluent English, satisfy the assigned age groups, not have completed the immunisations when residing in institutions or those not currently residing in Australia when interviewed (n=19, 1.8%). Missing, erroneous or irrelevant data that was cleaned and/or excluded are highlighted in table 1.

Descriptive statistics were first generated through univariate analysis to characterise the study population and contrast the young and old groups. Bivariate analysis using Pearson Chi-square or Fisher’s exact test for categorical data involving most variables were carried out as appropriate. A p-value of <0.05 was considered statistically significant. The odds ratios (OR) and 95% confidence intervals (CI) were also estimated. Multiple logistic regression was conducted to examine significant predictors of vaccine receipt found in bivariate analysis.

Statistical procedures were performed using SPSS version 20.0 (SPSS Inc. Chicago, IL, USA).

Table 1. Baseline characteristics of young and old participants.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Young Group (n=519)</th>
<th>Old Group (n=518)</th>
<th>Total (n=1037)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>258 (50.3)</td>
<td>325 (62.7)</td>
<td>583 (56.2)</td>
</tr>
<tr>
<td>Male</td>
<td>261 (49.7)</td>
<td>193 (37.3)</td>
<td>454 (43.8)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>20.39 (2.315)</td>
<td>78.45 (6.027)</td>
<td></td>
</tr>
<tr>
<td>Median (min to max)</td>
<td>20.00</td>
<td>78.00</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>18-30</td>
<td>70-95</td>
<td></td>
</tr>
<tr>
<td>Did you have immunisations when young?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>508 (98.6)</td>
<td>300 (66.1)</td>
<td>808 (83.4)</td>
</tr>
<tr>
<td>No</td>
<td>7 (1.4)</td>
<td>154 (33.9)</td>
<td>161 (16.6)</td>
</tr>
<tr>
<td>Immunisation status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>472 (96.3)</td>
<td>102 (24.6)</td>
<td>574 (63.4)</td>
</tr>
<tr>
<td>Low</td>
<td>18 (3.7)</td>
<td>313 (75.4)</td>
<td>331 (36.6)</td>
</tr>
<tr>
<td>Head of Household</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother</td>
<td>425 (83.3)</td>
<td>423 (77.2)</td>
<td>848 (80.3)</td>
</tr>
<tr>
<td>Father</td>
<td>82 (16.1)</td>
<td>47 (8.6)</td>
<td>129 (12.2)</td>
</tr>
<tr>
<td>Relative</td>
<td>3 (0.6)</td>
<td>78 (14.2)</td>
<td>81 (7.7)</td>
</tr>
<tr>
<td>Household head education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tertiary or more</td>
<td>383 (78.8)</td>
<td>67 (17.0)</td>
<td>450 (51.1)</td>
</tr>
<tr>
<td>Less than tertiary</td>
<td>103 (21.2)</td>
<td>327 (83.0)</td>
<td>430 (48.9)</td>
</tr>
<tr>
<td>Socioeconomic status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>434 (88.9)</td>
<td>168 (40.7)</td>
<td>602 (66.8)</td>
</tr>
<tr>
<td>Moderate-low</td>
<td>54 (11.1)</td>
<td>245 (59.3)</td>
<td>299 (33.2)</td>
</tr>
<tr>
<td>Number of siblings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤3</td>
<td>464 (94.7)</td>
<td>219 (52.8)</td>
<td>665 (75.0)</td>
</tr>
<tr>
<td>&gt;3</td>
<td>26 (5.3)</td>
<td>196 (47.2)</td>
<td>222 (25.0)</td>
</tr>
</tbody>
</table>

1 excluded missing/NA/other and those whose head of household was “Other” or “Head of institution”
Results

This research consists of combined data from two separate medical student cohorts undertaking this project during UNSW Semester 1 2012 and 2013. In total, data from 519 in the young group and 518 in the old group were included in the analysis after exclusions detailed above. The demographic profile is shown in Table 1. The numbers of female and male participants were approximately equal in the young group (female: n=258, 50.3% and n=325, 49.7% respectively), while the older group had more females than males (62.8% and 37.2% respectively). The mean age was 20.4 years (range: 18-30) in the young group and 78.5 years (range: 70-95) in the older group. Figure 1 highlights the percentage of participants with high and low immunisation in each age group.

Univariate analysis was conducted and found that in the young group, individuals who had the head of the household having an education tertiary or more were more likely to be highly immunised than those who had a head of the household who had not attained a tertiary education (OR: 2.87, 95%CI 1.04-7.94). In the old group, similar findings were found (OR: 2.13, 95%CI 1.19-3.80). Further univariate analysis found that gender, socioeconomic status and numbers of siblings in the family were not correlated with immunisation status in either of the age groups.

A multiple logistic regression was performed on the head of household education level with vaccination status to determine the unadjusted odds ratios (OR) with each incremental increase in education. Odds ratios of less than 1 indicated decreased likelihood of high immunisation compared with the reference group (Table 2, Figure 2). In the young group, a participant would be approximately 3.5 times more likely to be highly immunised if the head of the household had a tertiary education rather than a secondary education (OR = 3.43, CI95% = 1.09-10.81, p<0.05). The likelihood of a higher immunisation status between those with a secondary education compared to the TAFE/diploma was not statistically significant. In the old group, compared to an individual whose head of the household had a secondary education, an individual would be more likely to have a high immunisation status if the head of the household had a tertiary education (OR= 2.56, CI95% = 1.36-4.81, p<0.01; OR= 1.92) or a TAFE/diploma (CI95% = 1.02-3.61, p<0.05). Further logistic regression analysis found that childhood residence (Australia vs non-Australia) and gender played no significant impact on the association between childhood vaccination status and parental education (Table 2).

Table 2. Multiple logistic regression head of household education and number of disease immunised against, stratified by age.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Age groups</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Low (n=19)</td>
<td>High (n=491)</td>
<td>Unadjusted OR (95% CI)</td>
<td>Adjusted OR (95% CI)</td>
<td>Low (n=296)</td>
<td>High (n=98)</td>
<td>Unadjusted OR (95% CI)</td>
<td>Adjusted OR (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head of household education</td>
<td>Secondary</td>
<td>5</td>
<td>64</td>
<td>1.00(Ref)</td>
<td>0.83(0.28-3.01)</td>
<td>230</td>
<td>60</td>
<td>1.00 (Ref)</td>
<td>1.92 (1.02-3.61)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TAFE/diploma</td>
<td>5</td>
<td>53</td>
<td>*3.43(1.09-10.81)</td>
<td>0.96(0.36-3.23)</td>
<td>36</td>
<td>18</td>
<td>**2.56 (1.36-4.81)</td>
<td>**2.16(1.23-3.78)</td>
<td></td>
<td></td>
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*p-value <0.05 ** p-value <0.01 *** p-value<0.001

Figure 1. Immunisation status in the young and old group.
Discussion

A number of areas in Australia have estimated levels of vaccination coverage below the 95% required to prevent disease outbreaks (6). Consequently, in an attempt to find factors which predispose to low immunisation, a number of studies have examined the relationship between immunisation coverage and potential explanatory variables in Australia, with the strongest association found with parental education (7-12). By using a questionnaire, we have been able to explore the association between educational level of head of household and immunisation coverage across two generations to see the changes in such an association.

The results of this study found higher education levels of head of the household are significantly associated with higher immunisation coverage in both the young and old groups. This is consistent with multiple studies from Australia and other countries which ascertained that each level of maternal education attained above illiteracy increases the probability of a child being vaccinated (7-10). This study found similar results, with each level of education increasing the probability of high immunisation status in both the older and young group. Although our study did not differentiate between maternal or paternal education, a similar baseline ratio of maternal and paternal head of households was present in the two groups (Table 1). Due to the majority of the heads of households being the mother (average of 80.1% across two groups) our findings will likely be deviated towards the findings of studies with maternal education.

However, some studies have found post-secondary parental education to be negatively correlated with high immunisation rates in children (12, 13). The authors state that responder bias may have been present as there was a low response rate. Moreover, the respondents may have been more likely to have fully immunised children than non-responders. An interesting element of our study is that the recruitment method biased sampling towards higher education status in childhood households, as the sampling method was ad hoc enlistment by higher education students of interviewees from friends, family and acquaintances which resulted in the enlistment of better-educated participants. Correspondingly in our study, the numbers of low immunisation in the young group is small as would be expected in this higher educated population. Future studies with greater numbers of participants with parents of low educational status are warranted.

Figure 2. High immunisation status according to parental education level.

The authors are not aware of any previous study which has compared an old and young group in order to assess the changing association between child vaccination with parental education. Our study showed that five decades ago, the risk for low immunisation doubled in secondary educated parents compared to if they had a TAFE/Diploma. However, in today’s society, the increase in education from secondary to TAFE/Diploma is no longer significant in affecting child immunisation status. A possible explanation for this phenomenon may be due to the changing association between education and socioeconomic status. In the past a TAFE/diploma may have been useful for increasing socioeconomic status compared to those with a secondary education. However in more recent years, a TAFE/diploma only increases socioeconomic status to a small degree (14). Nonetheless, in both our young and the old groups, a tertiary education still remained significantly associated with higher immunisation rates, to an even greater degree in the younger group. This study highlights that the interaction between education level and vaccination is never static and is likely to change with key social changes. It is recommended that interventions and social policies should keep aware of this and adapt accordingly for optimal outcomes.

The stark increase in risk for low immunisation holds important clinical implications. For Australia, it has been estimated that interventions that increase immunisation coverage by only 2-5% may be enough to achieve herd immunity in some areas (11). Our study suggests that such interventions should focus on targeting parents with an educational background less than tertiary level. Moreover, an increasing benefit is likely with each decrease in education level targeted.

These findings may also be useful for other countries where the demographics for parental educational levels parallel to those seen old or young group in our study.

A limitation in our study is the recruitment method, which was ad hoc sampling of those known to the 550+ medical student interviewers and conducted in 2 separate years, and led to a partial sampling of the population. Another recognised limitation of this questionnaire-based study design is the possible recall bias. This is especially important here as we relied on recall of information regarding childhood from over 50 years ago in half the participants (15), where the error is likely to be more pronounced than in the younger generation.
Furthermore, participants may have counted the number of injections received in reporting the number of diseases immunised against. Certainly this would be more correct for the older group where one disease was not combined with another in a vaccine. However, in the younger group, if the participant received a combined vaccine, the number of injections received would not correlate with the number of vaccines received.

However, this under-representation may be partially compensated for the fact that many of the trivalent vaccines such as MMR require two injections. To minimise this recall error, the option of “Don’t know” as well as “NA” were given for participants to choose if they were uncertain of their answer.

A further limitation of this study was the difference in the number of available vaccinations in childhood, with more available for those in the young group. In the older group with a median age of 78 years, by the end of childhood (defined as 16 years, 1953), there were 4 diseases, which they could be vaccinated against: smallpox, tetanus, diphtheria and pertussis (16). Although collecting data from medical records would be more appropriate, such records for the participants in the old group were unavailable.

**Conclusion**

Despite these limitations, this study adds to the literature on this interesting issue. We have found that the education level of the head of household was shown to be significantly associated with immunisation coverage, which in turn suggests that parents with an educational background less than tertiary level could be targeted to encourage to have their children vaccinated in order to enhance immunisation coverage and therefore reduce child mortality.

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GLOBAL HEALTH

Are Malaysian Medical Students Prepared for a Disaster?

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Abstract

Objective: To assess the Concept, Knowledge, Attitude and Opportunity (CKAO) of Malaysian medical students in the field of disaster medicine.

DESIGN: Cross-sectional study.

Setting: Three medical universities in Malaysia.

Participants: Among the 405 students who took part in this research, 145 students had undergone an Accidents & Emergency posting (post-A&E group) while 260 students had not undergone A&E postings (pre-A&E group).

Findings: Mann-Whitney U test was used to test for significant differences between the pre-A&E and post-A&E group. There was significant difference in the Attitude (p=0.043) and Opportunity (p=0.033) scores between the pre-A&E and post-A&E group while Concept (p=0.065) and Knowledge (p=0.292) differences were not statistically significant.

Conclusion: The A&E posting changes the Attitudes of medical students toward disaster and provides them with Opportunities to be involved but does not improve their Concept or Knowledge. Disaster preparedness is insufficient among medical students in Malaysia.

The World Health Organisation (WHO) defines disaster as “a situation or event, which overwhelms the local capacity, necessitating a request for external assistance at a national or international level” (1). Despite being outside of the “Pacific Ring of Fire”, Malaysia has been hit by various natural and man-made disasters such as floods, landslides, droughts and even a tsunami. The Japanese Encephalitis (JE) outbreak in 1999, followed by the 2003 SARS outbreak and the Indian Ocean Tsunami in 2004 resulted in a significant number of deaths nationwide (2).

In any disaster, preparedness is a key determining factor for survival of victims. Healthcare personnel need to be prepared to execute disaster plans, in addition to the standard acute and long-term medical care (3). In the context of acute medical care, which focuses on the second phase of the tri-modal distribution of death (4), all house officers in Malaysia are required to be formally trained in cardiopulmonary resuscitation (CPR) and Basic Trauma Life Support (BTLS). Those successful will have the opportunity to undergo Acute Cardiac Life Support (ACLS) or Acute Trauma Life Support (ATLS)(5). The latter is relevant as trauma is the third most common cause of admission to a Malaysian Hospital (6).

Long-term care, on the other hand, begins immediately on the scene of the trauma, and continues until the patient regains full functional and mental capacity. Recognising the long-term impact of trauma resuscitation will reduce the risk of complications like spinal cord injuries (7) and post-traumatic stress disorders (8). Medical students are the future healthcare workforce. Disaster preparedness and response should therefore be a priority in their training (9). Many studies have been conducted within this scope; extending from curriculum design (10-12), attitude and awareness (13,14) to actual involvement in a real disaster (15,16). Nonetheless, a perusal of the literature on disaster preparedness of medical students in Malaysia revealed a dearth of reliable information or data published. Our study aimed to identify the levels of Concept (C), Knowledge (K), Attitude (A) and Opportunity (O) of Malaysian medical students with regard to disaster preparedness. The results of this study will serve as a foundation for further improvement in the training of future doctors.
Methodology

A cross-sectional study involving three Malaysian universities: Monash University Sunway Campus (MUSC), Universiti Putra Malaysia (UPM) and International Medical University (IMU) was conducted. Two groups of medical students from these universities were included in this study: (1) those that had completed their Accident & Emergency (A&E) posting (post-A&E group) and (2) those that had not (pre-A&E group). The post-A&E group were medical students who had undergone at least one formal posting in the emergency department as outlined in the emergency medicine curriculum of their respective universities.

Around 500 medical students from the three universities were approached and the questionnaire was administered from 7 September to 12 November 2012. During this period, 405 medical students responded.

Instrument and Data Collection

The instrument used in this study was a questionnaire (Appendix 1), which had been piloted on similar groups of post-A&E and pre-A&E medical students. The revised questionnaire had a total of 38 questions, divided into 4 sections: Concept, Knowledge, Attitude and Opportunity (CKAO) (see Figure 1).

- **Concept** was defined as a person’s understanding toward disasters and disaster medicine.
- **Knowledge** was defined as a person’s management skills and proficiency in the event of a disaster.
- **Attitude** was the reflection of a person’s manner toward disaster medicine.
- **Opportunity** was defined as the frequency of exposure to disaster-related activities.

Copies of the explanatory statement (Appendix 2) and questionnaire were sent to representatives in the respective universities, who in turn distributed the copies to consenting students. To avoid any form of coercion, the representatives were independent individuals who were not part of the research team. The self-administered questionnaires were completed anonymously, with consent being implied by completion and return of the questionnaire to the representatives.

Statistical analysis

The data collected was analysed using SPSS® Version 19.0 (Armonk, NY: IBM Corp). A descriptive analysis was used to summarise quantitative and qualitative variables. The demographics of the study population consisted of A&E posting, mean age, gender and medical year distribution. The students’ response to each component of the questionnaire was then analysed. In addition, a probability distribution analysis was performed for CKAO to determine any difference between the two groups.

Results

A total of 405 medical students took part in this research. One hundred and forty five students had undergone an A&E posting (post-A&E) while 260 students had not (pre-A&E) (Figure 2).

The mean ages of the post-A&E and pre-A&E groups were 23 and 22 years, respectively. In the post-A&E group, 68 (47%) were male. In the pre-A&E group, 126 (48%) were male.

Figure 3 shows the distribution of medical students based on their year of medical study. There were a total of 156 students in Year 3, 127 in Year 4 and 122 in Year 5.

Tables 1 to 4 show the frequency and percentage of correct and incorrect responses to each question in the Concept, Knowledge, Attitude and Opportunity (CKAO) components, respectively. A Kolmogorov normality test was used to check the skewness of the CKAO and total scores. Consequently, a nonparametric Mann Whitney U test was used to detect any significant differences between the two groups.

The maximum score for each component was Concept: 10, Knowledge: 10, Attitude: 13 and Opportunity: 5; with a total score (T) of 38. The median scores for post and pre-A&E for each aspect was shown in Table 5. The pre and post A&E median score for concept was 5 and 5, for knowledge was 5 and 5, for attitude was 11 and 10 and was 1 and 1 for opportunity.

This study found no significant difference in Concept (p=0.065) or Knowledge (p=0.292) scores between students who had undergone an A&E posting and those who had not. The median Concept score for both groups of students was 5 out of a total score of 10. Both groups also scored a median of 5 out of a total of 10 for Knowledge. Conversely, the Attitude scores revealed statistically significant differences between both groups, with the post-A&E group faring better (p=0.043). The post-A&E group had a better median Attitude score of 11 compared to 10 in the pre-A&E group. Although the median Opportunity score was the same in both populations, there was a significant difference, with post-A&E students performing better than pre-A&E students. The Total scores were significantly different (p=0.001) with a median of 23 in the post-A&E group and a median of 22 in the pre-A&E group.

Discussion

The lack of difference in Concept and Knowledge scores was surprising considering that one group underwent an A&E posting. This could perhaps be attributed to the lack of disaster medicine education and training in their medical curricula. In addition, emphasis placed on disaster medicine in university assessments may be insufficient or even absent.

The low median Concept score suggests that medical students have a poor awareness and understanding of disasters in Malaysia. It is shocking to discover that only 6.2% and 5.5% of pre-A&E and post-A&E students, respectively, actually know the four phases of disaster management. Furthermore, more than half of the pre-A&E and approximately 40% of the post-A&E students held the assumption that disasters in Malaysia were rare and isolated. This may suggest that relatively less effort is applied in learning disaster medicine compared to other fields of medicine.

Regrettably, more than a third of the pre-A&E and post-A&E students had the misconception that “911” was the Malaysian emergency hotline number (when it is “999”). This situation can also be seen in the United States where a study revealed that 85% of the students did not know whom to report a disaster to (14). This reflects the dearth of crucial, fundamental knowledge that may significantly affect the emergency response time in life-saving
situations.

This study also reveals that medical students are not familiar with the latest Malaysian cardiopulmonary resuscitation (CPR) guidelines as only 45.4% and 57.9% of pre-A&E and post-A&E students, respectively, knew the correct CPR sequence. Knowledge of triage was also inadequate as more than two-thirds of them thought that triage involved providing treatment. This finding on triage concurred with another study that showed less than 40% of medical students were able to triage mass casualty scenarios without prior ATLS lecture (17).

The post-A&E group fared better in the Attitude component. The A&E posting might have provided an insight into the seriousness and complexity of disaster medicine. This could result in a change in attitude, echoing a study conducted in the USA which revealed more positive attitudes after participation in a disaster seminar and drill (9). It is interesting to note that almost 90% of both groups of students believed that disaster management was important to know, but only about 40% of them would use the internet to obtain information on disaster preparedness. This could be attributed to their lack of interest in disaster medicine. Another possibility is that they were confident of their ability to assist in a disaster as more than two-thirds of the students thought that they could contribute medical assistance in a disaster. This finding corresponds to a study in the United States where 82% of the students believed that they were prepared to respond to a disaster (14).

Those who had completed their A&E postings might have been provided with more opportunities and priorities to participate in practical situations like drills and disaster relief work. Nearly 80% of clinical-year students did not have disaster medicine as part of their education curriculum which further highlights the inadequate exposure and opportunity for students to get involved in this field.

The median Total score was higher in students who had completed the A&E posting, which was an overall reflection of their higher median Attitude scores. The A&E posting was successful in changing medical students’ attitudes toward disaster medicine.

Generally, findings from this study concur with previously conducted international studies. A study conducted in Jabalpur, India on 375 medical undergraduates to evaluate their level of knowledge, attitude and practices of disaster preparedness and mitigation subsequently revealed knowledge inadequacy (13). Correspondingly, a study done among final-year medical students in Pakistan found that they were unprepared in assisting doctors during the Kashmir earthquake disaster (15).

**Strengths of the study**

There is a lack of information on disaster management in Malaysia. Literature review identified the issues of insufficient evaluation and review on the preparedness of the major stakeholders in disaster management. To date, there was only one study conducted in Malaysia which evaluated the level of knowledge and practice of Directive 20 (18) and none on medical students. This highlights the importance of our study in identifying the information gaps in disaster preparedness among future doctors.

An important strength of this study lies in the finding that despite having undergone an A&E posting, medical students still have a poor understanding of disaster concepts and knowledge. This strongly supports a review of disaster medicine teaching in the medical curriculum.

**Limitations of the study**

Several limitations of this study should be acknowledged. Due to the constraint of time and resources, this study was limited to only three medical universities. Thus, the results may not be representative of the entire Malaysian medical student population. Studies addressing this research question should have included a greater sample size and involved more Malaysian medical universities.

Another limitation relates to the use of self-administered questionnaires where there is always a potential for respondent errors. The respondents might have misunderstood the questions, and there was no opportunity for clarification from the researchers. With regard to data analysis, the grouping of “unsure” answers with the incorrect answers in the Knowledge section also serves as a limitation.

The findings of this study could not be compared with any
previous research on medical students in Malaysia. As a result, this study can only provide baseline information on the four components of Concept, Knowledge, Attitude and Opportunity of disaster preparedness in the Malaysian context.

**Future suggestions**

The findings of a study conducted in an Australian Hospital showed that limited education on disaster preparedness, lack of simulation training and actual hands-on experience resulted in inadequate preparedness of hospital staff to respond to disasters (19). We therefore strongly suggest that disaster education should begin early in medical school for medical students to be familiar with all aspects disaster management. The structure of the syllabus should encompass multidisciplinary efforts and include experts from various relevant fields in delivering the academic content (20).

Medical curricula and university lecturers should constantly be updated on the latest guidelines of the Basic Life Support (BLS) and Advanced Trauma Life Support (ATLS). Disaster drills should also be carried out in collaboration with teaching hospitals to enable the application of disaster medicine knowledge in simulated real-life situations.

The adequacy of the teaching of long-term care in disaster management, including aspects of public and mental health, in the medical curriculum should also be assessed. Failure to address these often-forgotten aspects of disaster management may pose communicable disease and mental health implications (21). Medical students should also be acquainted with support groups involved with the long-term care of disaster victims, particularly in areas of psychological health.

Collaboration between local medical student bodies like the Asian Medical Students’ Association (AMSA) Malaysia and with non-governmental organisations (NGOs) like the Malaysian Red Crescent Society (MRCs), St. John Ambulance and MERCY Malaysia would be beneficial. MERCY Malaysia, as an example, is a non-profit organisation whose work encompasses the provision of medical care, execution of activities for risk reduction and sustainable development in disasters (22). This collaboration would be of mutual benefit, giving medical students more opportunities to experience disaster management first-hand whilst providing NGOs with additional resources to manage disasters.

At present, there is a definite lack of research in disaster medicine in Malaysia. Therefore, the government should greatly encourage and provide grants to conduct more of such research in the future. In developing research in this area, the Disaster Research Nexus, established in Universiti Sains Malaysia (USM), would be a good model of research organisation and integration (23).

**Conclusion**

The evidence from this study suggests that the A&E posting changes the attitudes of medical students toward disaster and provides them with opportunities to be involved. However, it does not alter their concept of disaster medicine nor add to their knowledge. This implies that medical curricula do not have sufficient impact on concepts and knowledge of disaster medicine among students, despite their willingness to learn. More emphasis should be placed on equipping medical students with the knowledge to be ready in the event of a disaster.

In conclusion, disaster preparedness among medical students is insufficient. We strongly suggest that disaster education be specifically implemented in medical school curricula to ensure better handling of disasters in the future.

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